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    2 MAY 01
                CA/CAplus Indian patent publication number format defined
NEWS 3
        MAY 08
NEWS 4
        MAY 14
                RDISCLOSURE on STN Easy enhanced with new search and display
                fields
NEWS 5
        MAY 21
                BIOSIS reloaded and enhanced with archival data
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     6 MAY 21
                TOXCENTER enhanced with BIOSIS reload
        MAY 21 CA/CAplus enhanced with additional kind codes for German
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                patents
        MAY 22
                CA/CAplus enhanced with IPC reclassification in Japanese
NEWS 8
                patents
        JUN 27
                CA/CAplus enhanced with pre-1967 CAS Registry Numbers
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NEWS 10 JUN 29 STN Viewer now available
NEWS 11 JUN 29
                STN Express, Version 8.2, now available
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NEWS 13 JUL 02 LMEDLINE coverage updated
                SCISEARCH enhanced with complete author names
NEWS 14 JUL 02
NEWS 15 JUL 02
                CHEMCATS accession numbers revised
NEWS 16 JUL 02
                CA/CAplus enhanced with utility model patents from China
NEWS 17 JUL 16 CAplus enhanced with French and German abstracts
NEWS 18 JUL 18
                CA/CAplus patent coverage enhanced
NEWS 19 JUL 26 USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 20 JUL 30 USGENE now available on STN
NEWS 21 AUG 06 CAS REGISTRY enhanced with new experimental property tags
NEWS 22 AUG 06 BEILSTEIN updated with new compounds
                FSTA enhanced with new thesaurus edition
NEWS 23 AUG 06
                CA/CAplus enhanced with additional kind codes for granted
NEWS 24 AUG 13
                patents
                CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 25 AUG 20
NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
             CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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=> file reg

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# http://www.cas.org/support/stngen/stndoc/properties.html

#### => e raloxifene/cn RALOX LC/CN E1 1 E2 RALOX-A/CN 1 E3: 1 --> RALOXIFENE/CN E4 RALOXIFENE HYDROCHLORIDE/CN 1 E5 1 RALOZAM/CN E6 3 RALSTONITE/CN RALSTONITE (ALF2 (OH))/CN E7 1 RALSTONITE (ALF2(OH).1/2H2O)/CN E8 1 E9 1 RALTAT 10/CN RALTEGRAVIR POTASSIUM/CN E10 1 E11 1 RALTITREXED/CN E12 RALUBEN/CN

=> s e3

L1 1 RALOXIFENE/CN

=> d l1 1 ide

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN

RN 84449-90-1 REGISTRY

ED Entered STN: 16 Nov 1984

CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl] - (CA INDEX NAME)

OTHER NAMES:

CN Keoxifene

CN LY 139481

CN Raloxifene

CN [2-(4-Hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl][4-(2-(1-piperidinyl)ethoxy)phenyl]methanone

MF C28 H27 N O4 S

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HSDB\*, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK\*, PATDPASPC, PHAR, PROMT, PROUSDDR, RTECS\*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: WHO

## \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1751 REFERENCES IN FILE CA (1907 TO DATE)
38 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1763 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus
COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 8.25 8.46

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 13:29:27 ON 21 AUG 2007 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT. PLEASE SEE "HELP USAGETERMS" FOR DETAILS. COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

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FILE COVERS 1907 - 21 Aug 2007 VOL 147 ISS 9 FILE LAST UPDATED: 20 Aug 2007 (20070820/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.

They are available for your review at:

## http://www.cas.org/infopolicy.html => s l1 1763 L1 L2=> d scan L2 1763 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN CC 1-0 (Pharmacology) Osteoporosis treatment and limitations and perspectives TI review bisphosphonate raloxifene parathyroid hormone fall prevention stdisuse syndrome Bone, disease IT (fracture; osteoporosis treatment and limitations and perspectives) IT Anabolic agents Osteoporosis (osteoporosis treatment and limitations and perspectives) Diphosphonates IT RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (osteoporosis treatment and limitations and perspectives) 13598-36-2D, Phosphonic acid, alkylidenebis-derivs. ΙT RL: BSU (Biological study, unclassified); BIOL (Biological study) (Bisphosphonate; osteoporosis treatment and limitations and perspectives) 9002-64-6, Parathyroid hormone ΙT RL: BSU (Biological study, unclassified); BIOL (Biological study) (osteoporosis treatment and limitations and perspectives) **84449-90-1**, Raloxifene 129318-43-0 ITRL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (osteoporosis treatment and limitations and perspectives) HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1 L21763 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN 1-1 (Pharmacology) CC Validation of a novel HPLC method for the determination of Raloxifene and TI its pharmacokinetics in rat plasma Raloxifene detn plasma HPLC; liq chromatog Raloxifene plasma; ST pharmacokinetics Raloxifene plasma Blood plasma IT Pharmacokinetics (pharmacokinetics of Raloxifene in blood plasma of rats after oral dose) IT Blood analysis HPLC (validation of novel HPLC method for determination of Raloxifene and its pharmacokinetics in rat plasma) 84449-90-1, Raloxifene TТ RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study) (validation of novel HPLC method for determination of Raloxifene and its pharmacokinetics in rat plasma)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L2 1763 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN

CC 1-8 (Pharmacology)

TI Effect of genistein and raloxifene on vascular dependent platelet aggregation

qenistein raloxifene antiplatelet platelet aggregation blood vessel ST

Blood vessel IT

Cardiovascular system, disease

Platelet aggregation

Platelet aggregation inhibitors

(effect of genistein and raloxifene on vascular dependent platelet aggregation)

IT Estrogen receptors

> RL: BSU (Biological study, unclassified); BIOL (Biological study) (effect of genistein and raloxifene on vascular dependent platelet aggregation)

IT Phytoestrogens

> RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of genistein and raloxifene on vascular dependent platelet aggregation)

10102-43-9, Nitric oxide, biological studies 9001-84-7, Phospholipase A2 IT 35121-78-9, Prostacyclin

RL: BSU (Biological study, unclassified); BIOL (Biological study) (effect of genistein and raloxifene on vascular dependent platelet aggregation)

446-72-0, Genistein 84449-90-1, Raloxifene TT

> RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (effect of genistein and raloxifene on vascular dependent platelet aggregation)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> s l1/prep

1763 L1

4449106 PREP/RL

38 L1/PREP L3

(L1 (L) PREP/RL)

=> d 13 4 ibib abs

CAPLUS COPYRIGHT 2007 ACS on STN ANSWER 4 OF 38 L3

ACCESSION NUMBER:

2005:1180831 CAPLUS Full-text

DOCUMENT NUMBER:

145:356564

TITLE:

The advance of synthetic studies on selective estrogen

receptor modulators

AUTHOR(S):

Hu, Xiao; Zhu, Yujin; Yuan, Pengfei; Wu, Dan

CORPORATE SOURCE: '

Fourth Brigade of Pharmacy, Medical College of Chinese People's Armed Police Force, Tianjin, 300162, Peop.

Rep. China

SOURCE:

Wujing Yixueyuan Xuebao (2005), 14(2), 151-156

CODEN: WYXUA9; ISSN: 1008-5041 Wujing Yixueyuan Xuebao Bianjibu

PUBLISHER:

DOCUMENT TYPE:

Journal; General Review

LANGUAGE:

Chinese

A review on progress of synthesis of two series selective estrogen receptor AB modulators (SERMs): (phenyl)stilbenes and benzoheterocycles. A review on the synthesis of tamoxifen, droloxifene, raloxifene, toremifene, idoxifene, levormeloxifene and their derivs.

=> d 13 ibib abs 1-

YOU HAVE REQUESTED DATA FROM 38 ANSWERS - CONTINUE? Y/(N):y

L3 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2007:70746 CAPLUS Full-text

DOCUMENT NUMBER: 147:172240

TITLE: Control of pharmaceuticals and animal health products

in wastewater effluents from manufacturing sites

AUTHOR(S): Parke, Neil J.; Good, Nanci F.; Meyerhoff, Roger D.

CORPORATE SOURCE: Lilly Corporate Center, Eli Lilly and Co.,

Indianapolis, IN, 46285, USA

SOURCE: WEFTEC.05, Conference Proceedings, Annual Technical

Exhibition & Conference, 78th, Washington, DC, United States, Oct. 29-Nov. 2, 2005 (2005), 145-155. Water

Environment Federation: Alexandria, Va.

CODEN: 69JOAM

DOCUMENT TYPE: Conference; (computer optical disk)

LANGUAGE: English

In many cases, the discharge of pharmaceuticals and animal health products at bulk manufacturing, fill/finish, development and research operations may not be directly regulated with numeric limitations as a part of a facility's wastewater discharge permit. The biol. activity of these discharged compds., if not properly managed, may have the potential to impact the operation of an onsite or a municipal wastewater treatment plant, aquatic species in streams, rivers, oceans, or a drinking water source. An overview of the Eli Lilly and Company environmental protection program is provided, which shows how potential releases of active ingredients from its operations are managed to protect the environment.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1063108 CAPLUS Full-text

DOCUMENT NUMBER: 145:417029

TITLE: Methods for generating stably linked complexes

composed of homodimers, homotetramers or dimers of

dimers

INVENTOR(S): Chien, Hsing Chang; Goldenberg, David M.; McBride,

William J.; Rossi, Edmund A.

PATENT ASSIGNEE(S): IBC Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 105 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT NO.						KIN	D :	DATE			APPL	ICAT:	ION :	NO.		D	ATE	
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			CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
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PRIORITY APPLN. INFO.:
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                                            WO 2006-US25499
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                                            US 2006-864530P
                                                                    20061106
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The authors disclose dimerization and docking domain (DDD) sequences for the generation of stably tethered structures of defined compns., which may have multiple functionalities and/or binding specificities. The tethered constructs may be virtually any mol. or structure, such as antibodies, antibody fragments, antibody analogs or mimetics, aptamers, binding peptides, fragments of binding proteins, known ligands for proteins or other mols., enzymes, detectable labels or tags, therapeutic agents, toxins, pharmaceuticals, cytokines, interleukins, interferons, radioisotopes, proteins, peptides, peptide mimetics, polynucleotides, RNAi, oligosaccharides, natural or synthetic polymeric substances, nanoparticles, quantum dots, organic or inorg. compds., etc. In one example, a fusion construct of a DDD sequence with an anti-CEA Fd fragment was prepared and shown to target colorectal cancer in a xenograft model.

L3 ANSWER 3 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2006:958171 CAPLUS Full-text

DOCUMENT NUMBER:

147:9760

TITLE:

Synthesis of raloxifene hydrochloride

AUTHOR (S):

Song, Yan-ling; Zhao, Yan-fang; Meng, Yan-qiu; Gong,

Ping

CORPORATE SOURCE:

Shenyang Institute of Chemical Technology, Faculty of Pharmaceutical-Engineering, Shenyang, 110142, Peop.

Rep. China

SOURCE:

AB

Zhongguo Xinyao Zazhi (2005), 14(7), 882-884

CODEN: ZXZHA6; ISSN: 1003-3734

PUBLISHER:

Zhongguo Xinyao Zazhi Youxian Gongsi

DOCUMENT TYPE:

Journal Chinese

LANGUAGE:

The synthesis of raloxifene hydrochloride [i.e., [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-piperidinyl)ethoxy]phenyl]methan one hydrochloride] is reported. The target compound was synthesized from 3-methoxybenzenethiol and 4-methoxy- $\alpha$ -bromo acetophenone via five steps, including substitution, cyclization, Friedel-Crafts reaction, di-Me reaction and salt formation. The structure of the target compound was confirmed by IR, 1H-NMR and MS. This synthetic route required mild conditions and provided an improved yield and was easily controlled.

L3 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:1180831 CAPLUS Full-text

DOCUMENT NUMBER:

145:356564

TITLE:

The advance of synthetic studies on selective estrogen

receptor modulators

AUTHOR(S):

Hu, Xiao; Zhu, Yujin; Yuan, Pengfei; Wu, Dan

CORPORATE SOURCE:

Fourth Brigade of Pharmacy, Medical College of Chinese

People's Armed Police Force, Tianjin, 300162, Peop.

Rep. China

SOURCE:

L3

Wujing Yixueyuan Xuebao (2005), 14(2), 151-156

CODEN: WYXUA9; ISSN: 1008-5041

PUBLISHER:

Wujing Yixueyuan Xuebao Bianjibu Journal; General Review

DOCUMENT TYPE: Journal; G

LANGUAGE: Chinese

AB A review on progress of synthesis of two series selective estrogen receptor modulators (SERMs): (phenyl)stilbenes and benzoheterocycles. A review on the synthesis of tamoxifen, droloxifene, raloxifene, toremifene, idoxifene, levormeloxifene and their derivs.

2005:708484 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER: 143:221841

Estrogen receptor ligands. Dihydrobenzoxathiin SERAMs TITLE:

with an optimized antagonist side chain

Blizzard, Timothy A.; DiNinno, Frank; Chen, Helen Y.; AUTHOR (S):

Kim, Seongkon; Wu, Jane Y.; Chan, Wanda; Birzin, Elizabeth T.; Yang, Yi Tien; Pai, Lee-Yuh; Hayes, Edward C.; DaSilva, Carolyn A.; Rohrer, Susan P.;

Schaeffer, James M.; Hammond, Milton L.

Merck Research Laboratories, Rahway, NJ, 07065, USA CORPORATE SOURCE:

Bioorganic & Medicinal Chemistry Letters (2005), SOURCE:

15(17), 3912-3916

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal English LANGUAGE:

CASREACT 143:221841 OTHER SOURCE(S):

An optimized side chain for dihydrobenzoxathiin SERAMs was discovered and attached to four dihydrobenzoxathiin platforms. The novel SERAMs show

exceptional estrogen antagonist activity in uterine tissue and an MCF-7 breast

cancer cell assay.

THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS REFERENCE COUNT: 27

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:451379 CAPLUS Full-text

DOCUMENT NUMBER: 142:487547

TITLE: Antiresorptive mutual salt of raloxifene and

bisphosphonic acid

Ha, Tae Hee; Kim, Won Jeoung; Yun, Sangmin; Kim, Cheol INVENTOR (S):

Kyung; Kim, Han Kyong; Suh, Kwee-Hyun; Lee, Gwan Sun

Hanmi Pharm. Co., Ltd., S. Korea PATENT ASSIGNEE(S):

SOURCE: PCT Int. Appl., 26 pp.

CODEN: PIXXD2

Patent DOCUMENT TYPE: English LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

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US 2007082871					A1		2007	0412	1	US 20	006-	5791	99		2	0060	512
PRIORITY APPLN. INFO.:							•		]	KR 20	003-	8049	4	7	A 20	0031	114
•									1	WO 2	004-1	KR29	54	1	N 2	0041	115

OTHER SOURCE(S): MARPAT 142:487547

The mutual salt of raloxifene and bisphosphonic acid exhibits unexpectedly synergistic effects of two components to enhance bone mineral d. (BMD), control blood-calcium d., and lower the serum cholesterol level. For example, 3.2 g of alendronic acid was mixed with 5.0 g of raloxifene in 75 mL of ethanol/75 mL of water to obtain 6.5 g of raloxifene alendronate pentahydrate. A soft or hard capsule was prepared containing raloxifene alendronate pentahydrate 30 mg, lactose 215 mg, magnesium stearate 2 mg, and colloidal silica 3 mg. When given to female rats, the mutual salt of raloxifene and alendronic acid markedly enhanced BMD, bone stiffness, trabecular volume and bone volume, and also effectively controlled the blood cholesterol and calcium level through the synergic effects of its two components, as compared with the individual raloxifene hydrochloride or alendronate.

REFERENCE COUNT:

4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2004:617920 CAPLUS Full-text

DOCUMENT NUMBER:

142:463529

TITLE:

Synthesis of raloxifene hydrochloride Gong, Ping; Zhao, Yanfang; Wang, Dun

CORPORATE SOURCE:

School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, Peop.

Rep. China

SOURCE:

Shenyang Yaoke Daxue Xuebao (2003), 20(2), 111-113

CODEN: SYDXFF; ISSN: 1006-2858

PUBLISHER:

AUTHOR(S):

Shenyang Yaoke Daxue Xuebao Bianjibu

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

OTHER SOURCE(S):

CASREACT 142:463529

AB Raloxifene hydrochloride, which is a selective estrogen receptor modulator, was synthesized from 3-methoxybenzenethiol and 2-bromo- 4'-methoxyacetophenone by etherification, cyclization in the presence of polyphosphoric acid, hydrolysis with HBr/HOAc to obtain 6-hydroxy- 2-(4-hydroxyphenyl)benzothiophene, acylation with acetic anhydride, acylation with 4-[2-(1-piperidinyl)ethoxy]benzoyl chloride in the presence of AlCl3, saponification with 5M NaOH solution in methanol, and saltification with HCl. The overall yield was 10.0%, and its structure was confirmed by MS, 1H NMR, 13C NMR.

L3 ANSWER 8 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2004:292022 CAPLUS Full-text

DOCUMENT NUMBER:

140:309411

TITLE:

Pharmaceutical compositions comprising raloxifene acid

addition salts and/or solvates

INVENTOR(S):

Karup, Gunnar Leo; Pedersen, Soren Bols

PATENT ASSIGNEE(S):

A/S Gea Farmaceutisk Fabrik, Den.

SOURCE:

PCT Int. Appl., 64 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

T: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004029046	A2	20040408	WO 2003-DK645	20030930
WO 2004029046	A3	20041014		

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PRIORITY APPLN. INFO.:
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OTHER SOURCE(S): MARPAT 140:309411

Raloxifene acid addn. salts or solvates thereof, having improved dissoln. properties in media comprising hydrochloric acid are described, compared with similar prepns. based on raloxifene or raloxifene-hydrochloride. The disclosed acid addition salts or solvates thereof show an improved bioavailability in media comprising hydrochloric acid, such as the gastric The acid addition salts or solvates thereof are addition salts or solvates of raloxifene and a pharmaceutically acceptable acid selected among succinic acid, lactic acid, malonic acid or sulfuric acid. Further, crystalline forms of the raloxifene salts and solvates thereof are disclosed. The raloxifene acid addition salts and/or solvates thereof are useful for the preparation of pharmaceutical composition for oral administration capable of fast and reliable release of the active ingredients in the stomach of the patient, in particular for the treatment of cancer or osteoporosis, or for inhibiting cartilage degradation A new method for preparation of raloxifene lactate is also disclosed. Thus, raloxifene malonate was prepared by the reaction of raloxifene-HCl with malonic acid in propanol-water solution The product was characterized by IR spectra and x-ray diffraction.

L3 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:269853 CAPLUS Full-text

ACCESSION NUMBER: 2004:26985 DOCUMENT NUMBER: 140:309370

TITLE: Amino acid and peptide carriers for oral delivery of

active agent

INVENTOR(S): Piccariello, Thomas; Kirk, Randal J.; Olon, Lawrence

Р.

PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA

Patent

SOURCE: U.S. Pat. Appl. Publ., 176 pp., Cont.-in-part of U.S.

Pat. Appl. 2002 128,177.

CODEN: USXXCO

DOCUMENT TYPE:

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 24

PAT	TENT NO.	KIND	DATE	APPLICATION NO.	DATE
US	2004063628	A1	20040401	US 2002-156527	20020529
US	7060708	B2	20060613		
` WO	2000052078	A1	20000908	WO 2000-US5693	20000306

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US 2000-248712P
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US 2000-248733P
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US 2000-248748P
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US 2001-959396
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US 2002-358368P
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                        20030224
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WO 2003-US5525
WO 2003-US5526
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WO 2003-US17009
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US 2003-507012P
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US 2004-567800P
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US 2004-567802P
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US 2004-568011P
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US 2004-923088
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US 2004-923257
                     A2 20040823
US 2004-953110
                     A2 20040930
US 2004-953111
                     A2 20040930
                     A2 20040930
US 2004-953116
US 2004-953119
                     A2 20040930
US 2004-955006
                     A2 20040930
WO 2004-US32131
                     A2 20040930
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The present invention relates to oral delivery systems of active agent, and more specifically to compns. that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for oral administration of conjugated active agent compns. For example, a polyserine-furosemide conjugate was prepared and its in vivo performance was examined Compared to parent furosemide, the conjugate showed a sustained drug release. The 9 h serum level of the polyserine-furosemide conjugate was 95.5% of its 3

h level, whereas the 9 h serum level of the parent drug was only 59.8% of its 3 h level.

ANSWER 10 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2003:726588 CAPLUS Full-text

DOCUMENT NUMBER:

139:345292

Nitrosation, nitration, and autoxidation of the selective estrogen receptor modulator raloxifene by

nitric oxide, peroxynitrite, and reactive

nitrogen/oxygen species

AUTHOR (S):

Toader, Violeta; Xu, Xudong; Nicolescu, Adrian; Yu, Linning; Bolton, Judy L.; Thatcher, Gregory R. J.

CORPORATE SOURCE:

Department of Medicinal Chemistry and Pharmacognosy,

College of Pharmacy, University of Illinois at

Chicago, Chicago, IL, 60612-7231, USA

SOURCE:

Chemical Research in Toxicology (2003), 16(10),

1264-1276

CODEN: CRTOEC; ISSN: 0893-228X

PUBLISHER:

American Chemical Society

DOCUMENT TYPE:

Journal English

LANGUAGE:

The regulation of estrogenic and antiestrogenic effects by selective estrogen AB receptor modulators (SERMs) provides the basis for use in long-term therapy in cancer chemoprevention and postmenopausal osteoporosis. However, the evidence for carcinogenic properties within this class requires study of potential

pathways of toxicity. There is strong evidence for the elevation of cellular levels of NO in tissue treated with SERMs, including the benzothiophene derivative, raloxifene, in part via up-regulation of nitric oxide synthases. Therefore, the reactions of  $17\beta$ -estradiol (E2), raloxifene, and an isomer with NO, peroxynitrite, and reactive nitrogen/oxygen species (RNOS) generated from NO2-/H2O2 systems were examined Peroxynitrite from bolus injection or slow release from higher concns. of 3-morpholinosydnonimine (SIN-1) reacted with the benzothiophenes and E2 to give aromatic ring nitration, whereas peroxynitrite, produced from the slow decomposition of lower concns. of SIN-1, was relatively unreactive toward E2 and yielded oxidation and nitrosation products with raloxifene and its isomer. The oxidation and nitrosation products formed were characterized as a dimer and quinone oxime derivative Interestingly, the reaction of the benzothiophenes with NO in aerobic solution efficiently generated the same oxidation products. Stable quinone oximes are not unprecedented but have not been previously reported as products of RNOSmediated metabolism The reaction of qlutathione (GSH) with the quinone oxime gave both GSH adducts from Michael addition and reduction to the corresponding o-aminophenol. The ready autoxidn. of raloxifene, observed in the presence of

NO, is the first such observation on the reactivity of SERMs and is potentially a general phenomenon of significance to SERM chemical toxicol.

REFERENCE COUNT:

THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 11 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3 2003:491620 CAPLUS Full-text

89

ACCESSION NUMBER: DOCUMENT NUMBER:

139:179942

TITLE:

Synthesis of Constrained Raloxifene Analogues by Complementary Use of Friedel-Crafts and Directed

Remote Metalation Reactions

AUTHOR (S):

Kalinin, Alexey V.; Reed, Mark A.; Norman, Bryan H.;

Snieckus, Victor

CORPORATE SOURCE:

Department of Chemistry, Queen's University, Kingston,

ON, K7L 3N6, Can.

SOURCE:

Journal of Organic Chemistry (2003), 68(15), 5992-5999

CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: LANGUAGE: Journal English

OTHER SOURCE(S):

CASREACT 139:179942

GI

### \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

New constrained heterocyclic analogs of Raloxifene, I [R1 = 2-(1-piperidinyl)ethoxy, R2 = H; R1 = H, R2 = 2-(1-piperidinyl)ethoxy] and II, were prepared by complementary Directed remote Metalation (DreM)/Friedel-Crafts cyclization approaches. Utilization of a benzylidene-thiolactone rearrangement was successfully implemented to construct benzothiophenes III (R3 = Me2CH, R4 = MeO; R3 = Me, PhCH2, R4 = Et2N) in good yields. Selective deprotection of III (R3 = Me2CH, R4 = MeO; R3 = PhCH2, R4 = Et2N) induced by complexation was followed by trifluoromethylsulfonylation and Suzuki-Miyaura cross coupling with 3-[2-(1-piperidinyl)ethoxy]phenyl dioxaborolane to give the corresponding 2,4-diaryl-substituted benzothiophenes with methoxycarbonyl or diethylcarbamoyl group in the 3 position. Treatment of the latter with BCl3 or with excess LDA induced an intramol. para or ortho cyclization and concomitant double deprotection to furnish I. Similar sequence starting from III (R3 = Me, R4 = Et2N) afforded the constrained analog II.

REFERENCE COUNT:

THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2002:408662 CAPLUS Full-text

DOCUMENT NUMBER:

136:401637

TITLE:

Preparation of 3-arylbenzothiophenes by

cyclodehydration of phenylthioacetophenones using

activated clay or zeolite catalysts.

INVENTOR(S):

Luke, Wayne Douglas; Sanderson, Heidi Ann; Zheng, Hua

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

PCT Int. Appl., 26 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

JM. COUNT: 1

PA	rent :	NO.			KIN	<b>D</b> :	DATE		1	APPL	ICAT	ION I	NO.	•	D	ATE	
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WO	2002	0422	89		A2		2002	0530	1	WO 2	001-	US42	940		2	0011	114
WO	2002	0422	89		<b>A</b> 3		2002	0906									
WO	2002	0422	89		A8		2004	0212									
	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	ΒZ,	CA,	CH,	CN,
		CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	ES,	FI,	GB,	GD,	GE,	GH,
	GM, HR, 1		HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	ΚP,	KR,	ΚZ,	LC,	LK,	LR,	
	LS, LT, L		LU,	LV,	MA,	·MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PH,	PL,	
		PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TR,	TT,	TZ,	UA,	UG,
		US,	UZ,	VN,	ΥU,	ZA,	ZW										
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		KZ,	MD,	RU,	ТJ,	TM,	AT,	BE,	CH,	CY,	DE,	DK,	ES,	FI,	FR,	GB,	GR,
		ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,
		GQ,	GW,	ML,	MR,	NE,	SN,	TD,	TG								
AU	AU 2002030409						2002	0603		AU 2	002-	3040	9		2	0011	114

US 2004132775 A1 20040708 US 2003-415569 20030922

US 6921827 B2 20050726

PRIORITY APPLN. INFO.: US 2000-253212P P 20001127

WO 2001-US42940 W 20011114

OTHER SOURCE(S): CASREACT 136:401637; MARPAT 136:401637

GΙ

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Title compds. (I; R1, R2 = H, protecting group) were prepd. by cyclodehydration of phenylthioacetophenones (II; variables as above) in the presence of acid activated clays or acid activated zeolites and in the presence of solvents. Thus, PhMe, α-(3-methoxyphenylthio)-4-methoxyacetophenone, and "acid-activated clay" (Engelhard X-9107) were combined and refluxed 2 h using a Dean Stark trap. By HPLC the product mixture consisted of 96.7% 6-methoxy-3-(4-methoxyphenyl)benzo[b]thiophene, 1.1% 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene, 2.1% 4-methoxy-3-(4-methoxyphenyl)benzo[b]thiophene, and 0.1% 4-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene.

L3 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:408636 CAPLUS Full-text

DOCUMENT NUMBER: 136:401533

TITLE: Coupling reaction process for preparing

 $\alpha$ -(3-arylthio)acetophenones from thiophenol derivs. and  $\alpha$ -(leaving group)-substituted

acetophenones

INVENTOR(S): Luke, Wayne Douglas; Sanderson, Heidi Ann; Zheng, Hua

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 17 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002042261	A2	20020530	WO 2001-US42939	20011114
WO 2002042261	A3	20030306		
W: AE, AG,	AL, AM, AT	, AT, AU, A	Z, BA, BB, BG, BR,	BY, BZ, CA, CH,
CN, CO,	CR, CU, CZ	, CZ, DE, DI	E, DK, DK, DM, DZ,	EC, EE, EE, ES,
FI, FI,	GB, GD, GE	, GH, GM, HI	R, HU, ID, IL, IN,	IS, JP, KE, KG,
KP, KR,	KZ, LC, LK	, LR, LS, LT	r, Lu, Lv, MA, MD,	MG, MK, MN, MW,
MX, MZ,	NO, NZ, PH	, PL, PT, RO	O, RU, SD, SE, SG,	SI, SK, SK, SL,
TJ, TM,	TR, TT, TZ	, UA, UG, US	S, UZ, VN, YU, ZA,	ZW, AM, AZ, BY,
KG, KZ,	MD, RU	•		
RW: GH, GM,	KE, LS, MW	, MZ, SD, SI	L, SZ, TZ, UG, ZW,	AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM; GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002028593 20020603 AU 2002-28593 20011114 PRIORITY APPLN. INFO.:

US 2000-253073P 20001127 WO 2001-US42939 W 20011114

OTHER SOURCE(S): CASREACT 136:401533; MARPAT 136:401533

GΙ

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 $\alpha$ -(3-Arylthio)acetophenones [I; R1, R2 = H, hydroxy-protecting group; e.g.,  $\alpha$ -AB (3-methoxyphenylthio)-4-methoxyacetophenone] are prepared in high yield and selectivity by the coupling of a thiophenol derivative 3-(R10)C6H4SH (e.g., 3methoxybenzenethiol) in an aqueous alkaline (e.g., KOH) solvent (e.g., Et acetate) with an aromatic ketone LCH2COC6H4(OR2)-4 (L = leaving group; e.g.,  $\alpha$ -chloro-4-methoxyacetophenone).

CAPLUS COPYRIGHT 2007 ACS on STN ANSWER 14 OF 38

ACCESSION NUMBER:

2001:283971 CAPLUS Full-text

DOCUMENT NUMBER:

134:300772

TITLE:

Glycosides and orthoester glycosides of raloxifene and

analogues and the use thereof

INVENTOR(S):

Holick, Michael Francis; Ramanathan, Halasya

PATENT ASSIGNEE(S):

Strakan Group PLC, UK PCT Int. Appl., 28 pp.

SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

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CR, CU,	CZ, I	DE,	DK,	DM,	DZ,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,	HR,
HU, ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	ΚP,	KR,	ΚZ,	LC,	LK,	LR,	LS,	LT,
			MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PL,	PT,	RO,	RU,
SD, SE, SG,		SI,	SK,	SL,	TJ,	TM,	TR,	TT,	ΤZ,	UA,	UG,	US,	UΖ,	VN,
YU, ZA,	ZW, Z	AM,	ΑZ,	BY,	KG,	KZ,	MD,	RU,	ТJ,	TM				
GH, GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZW,	AT,	BE,	CH,	CY,
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• • • •		CM,	GΑ,	GN,	GW,	ML,	MR,	ΝE,	SN,	TD,	TG			
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OTHER SOURCE(S): MARPAT 134:300772

Raloxifene and raloxifene analog qlycosides and orthoester glycosides afford greater serum bioavailability of the hydroxylated parent compound, and are useful for treating or preventing a number of conditions that may be treated with an anti-estrogenic or an anti-androgenic compound To a mixture of 0.5 g

raloxifene and 1.6 g silvér silicate in dry acetonitrile was added 3 g mol. sieves and stirred for 20 min. To the above suspension was added 1.0 g acetobromo- $\alpha$ -D-glucose and heated for 2 h at 60°, then filtered through a bed of silica gel and eluted with dichloromethane and methanol. The yellow eluent was concentrated under vacuum to obtain yellowish crystals. Proton NMR spectrum showed the crystals were consisted of 2 possible monoglucosides and a doubly glycosylated product.

REFERENCE COUNT:

THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 38 ACCESSION NUMBER:

CAPLUS COPYRIGHT 2007 ACS on STN

1999:440767 CAPLUS Full-text

DOCUMENT NUMBER:

131:228604

TITLE:

Synergistic methodologies for the synthesis of 3-aroyl-2-arylbenzo[b]thiophene-based selective

estrogen receptor modulators. Two concise syntheses of

raloxifene

AUTHOR (S):

Bradley, David A.; Godfrey, Alexander G.; Schmid,

Christopher R.

CORPORATE SOURCE:

Chemical Process Research and Development, A Division of Eli Lilly and Company, Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN,

46285-4813, USA

SOURCE:

Tetrahedron Letters (1999), 40(28), 5155-5159

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER:

Elsevier Science Ltd.

DOCUMENT TYPE:

Journal

LANGUAGE: English ΔR

Functionalized benzo[b] thiophene intermediates are prepd. which allow fully independent elaboration of the 2-aryl position or the tether position of benzo[b]thiophene-based selective estrogen receptor modulators (SERMs). Two

concise syntheses of the SERM raloxifene (Evista) are presented.

REFERENCE COUNT:

32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 16 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1999:188589 CAPLUS Full-text

DOCUMENT NUMBER:

130:311683

TITLE:

Novel nonsteroidal selective estrogen receptor

modulators. Carbon and heteroatom replacement of

oxygen in the ethoxypiperidine region of raloxifene Schmid, Christopher R.; Sluka, James P.; Duke, Kristen AUTHOR(S):

M.; Glasebrook, Andrew W.

CORPORATE SOURCE:

Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN,

46285, USA

SOURCE:

Bioorganic & Medicinal Chemistry Letters (1999), 9(4),

523-528

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER:

Elsevier Science Ltd.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

Compds. were synthesized where oxygen in the ethoxypiperidine region of AB raloxifene is replaced with carbon, sulfur, or nitrogen linkages. aza-substituted compds. were prepared by novel methodol. The compds. were evaluated in vitro as selective estrogen receptor modulators (SERMs). Calcns. suggested the compds. exhibit an ER- $\alpha$  binding affinity/conformational energy

REFERENCE COUNT:

relationship.

THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS 31 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 17 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3

ACCESSION NUMBER: 1999:71534 CAPLUS Full-text

DOCUMENT NUMBER: 130:196550

Nucleophilic aromatic substitution on TITLE:

> 3-aroyl-2-arylbenzothiophenes. Rapid access to raloxifene and other selective estrogen receptor

> > modulators

Schmid, Christopher R.; Sluka, James P.; Duke, Kristin AUTHOR(S):

Lilly Research Laboratories, A Division of Eli Lilly CORPORATE SOURCE:

and Company, Lilly Corporate Center, Indianapolis, IN,

46285-4813, USA

Tetrahedron Letters (1999), 40(4), 675-678 SOURCE:

CODEN: TELEAY; ISSN: 0040-4039

Elsevier Science Ltd. PUBLISHER:

DOCUMENT TYPE: Journal LANGUAGE: English

CASREACT 130:196550 OTHER SOURCE(S):

Versatile, mild and high yielding methods for nucleophilic arom. substitution

of 2-dialkylamino-1-ethoxides and related nucleophiles on 3-aroyl-2-

arylbenzothiophene nuclei are presented. A short synthesis of raloxifene is

detailed.

REFERENCE COUNT: THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS 28

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 18 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1998:721690 CAPLUS Full-text

DOCUMENT NUMBER:

130:3769

Processes for preparing benzothiophenes TITLE:

McGill, John McNeil, III; Misner, Jerry Wayne; Zhang, INVENTOR(S):

Tony Yantao

PATENT ASSIGNEE(S):

SOURCE:

Eli Lilly and Co., USA PCT Int. Appl., 26 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

PR:

English

FAMILY ACC. NUM. COUNT:

	TENT				KINI		DATE			APPL	ICAT	ION 1	NO.		D	ATE	
	9849						1998	1105	,	 WO 1	.998-	US85	 09		1	9980	 428
		AL,															
		GM,	GW,	HU,	ID,	IL,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	LK,	LR,	LS,
		LT,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,	RO,	RU,	SD,	SG,	SI,
		SK,	SL,	TJ,	TM,	TR,	TT,	UA,	UG,	US,	UΖ,	VN,	YU,	ZW			
	RW:	GH,	GM,	KE,	LS,	MW,	SD,	SZ,	UG,	ZW,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,
		GN,	ML,	MR,	NE,	SN,	TD,	TG			•						
CA	2287	943			A1		1998	1105	(	CA 1	998-	2287	943		1	9980	128
AU	9872	613			Α		1998	1124		AU 1	998-	7261	3		1	99804	128
BR	9809	439			Α		2000	0613	]	BR 1	998-	9439			1	99804	128
	7 2000									HU 2	000-	3187			1	99804	128
	2001										998-						
US	6090	949			Α		2000	0718	1	US 1	998-	6949	7		1	99804	129
EP	8755										998-					-	
	R:	AT,						FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	MC,	PT,
		•	•	•	LV,	•									_		
	9909				Α		2000	0331								9991	
RIORIT	Y APP	LN.	INFO	. :					1	US 1	997-	4517	7P	]	P 1:	99704	130

OTHER SOURCE(S): CASREACT 130:3769; MARPAT 130:3769

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The title compds. [I; Y = Cl, Br, I, SO2(Cl-4 alkyl), etc.] were prepd. by reacting benzo[b]thiophene II [R51, R52 = hydroxy protecting groups] with benzoyl chloride III [R8 = acyl activating group] in the presence of a boron trihalide such as BCl3. Compds. I were reacted further with an amine HNR6R7 [R6, R7 = Cl-4 alkyl; NR6R7 = piperidino, pyrrolidino, morpholino, etc.] to produce benzothiophenes IV and their salts.

REFERENCE COUNT:

4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1998:721501 CAPLUS Full-text

DOCUMENT NUMBER:

130:3768

TITLE:

Demethylation process for preparing benzo[b]thiophenes

Hoard, David Warren; Luke, Wayne Douglas

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA Eur. Pat. Appl., 13 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

INVENTOR(S):

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND DATE	APPLICATION NO.	DATE
EP 875511	A1 19981104	EP 1998-303345	19980429
R: AT, BE, CH,	DE, DK, ES, FR, GB,	, GR, IT, LI, LU, NL,	SE, MC, PT,
IE, SI, LT,	LV, FI, RO		
CA 2236254	A1 19981030	CA 1998-2236254	19980427
JP 11005789	A 19990112	JP 1998-118628	19980428
US 5994547	A 19991130	US 1998-69500	19980429
PRIORITY APPLN. INFO.:		US 1997-45156P	P 19970430
OTHER SOURCE(S):	CASREACT 130:3768;	MARPAT 130:3768	
GT			

The prepn. of benzo[b]thiophenes I [R1, R2 = C1-4 alkyl; NR1R2 = piperidino, pyrrolidino, etc.] by the acylation of alkoxy protected starting materials followed by demethylation of II using essentially odorless thiol compound (2-methyl-5-t-Bu-benzenethiol) are provided herewith. Demethylation may be carried out in the same reaction vessel without isolation of the acylated, protected material.

REFERENCE COUNT:

10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1998:719257 CAPLUS Full-text

DOCUMENT NUMBER:

130:3765

TITLE:

Intermediates and processes for preparing

benzo[b] thiophenes

INVENTOR(S):

Misner, Jerry Wayne; Schmid, Christopher Randall

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

PCT Int. Appl., 59 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PA	PATENT NO.					D	DATE		1	APPL	ICAT	ION	NO.		D	ATE	
						<b>-</b> .									-		
WO	9848	793			<b>A</b> 1		1998	1105	1	WO 1:	998-1	US85	10		1:	9980	428
	W:	AL,	AM,	AT,	AU,	ΑZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CU,	CZ,	DE,
		DK,	EE,	ES,	FI,	GB,	GE,	GH,	GM,	GW,	HU,	ID,	IL,	IS,	JP,	ΚE,	KG,
		KP,	KR,	ΚZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX,
		NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	TJ,	TM,	TR,	TT,
		UA,	UG,	US,	UZ,	VN,	YU,	ZW								•	
	RW:	GH,	GM,	KE,	LS,	MW,	SD,	SZ,	UG,	ZW,	ΑT,	BE,	CH,	CY,	DE,	DK,	ES,
		FI,	FR,	GB,	GR,	IE,	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,
							NE,				•						
CA	2287	922		•	A1	•	1998	1105		CA 1:	998-	2287	922		1:	9980	428
	9872															980	
ΕP	9790	76			<b>A</b> 1		2000	0216	]	EP 1:	998-	9199	36		1:	9980	428
	R:	AT,	BE,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	NL,	SE,	PT,	ΙE,	FI		
JP	JP 2001523253			•	T	•	2001	1120		JP 1:	998-!	5472	78 <sup>.</sup>	•	1:	9980	428
US	6018	056			Α		2000	0125	1	US 1:	998-	6927	8		19	9980	429

PRIORITY APPLN. INFO.: US 1997-45131P

WO 1998-US8510

P 19970430 W 19980428

OTHER SOURCE(S):

CASREACT 130:3765; MARPAT 130:3765

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. [I-III; R = hydroxy protecting group; Y = CO2H, CO2(C1-4 alkyl), C(halo), etc.; A = OH, halo, NO2, etc.; R1 = hydroxy protecting group, H], useful intermediates in the further preparation of pharmaceutical benzo[b]thiophenes, were prepared Thus, reaction of 6-methoxythianaphthen-2-one with p-anisaldehyde in the presence of piperidine in EtOH and THF afforded 45% E/Z-I [R = Me].

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1998:161136 CAPLUS Full-text

DOCUMENT NUMBER:

128:221639

TITLE:

Preparation of amorphous benzothiophenes for

pharmaceuticals

INVENTOR (S):

Cuff, George W.; Thakkar, Arvind L.

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA; Cuff, George W.; Thakkar,

Arvind L.

SOURCE:

PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PAT	CENT :										LICAT						
WO	9808										 1997-						
	W:	AL,	AM,	AU,	ΑŻ,	BA,	BB,	BG,	BR,	BY	, CA,	CN,	CU,	CZ,	EE,	GE,	GH,
		HU,	IL,	IS,	JP,	KE,	KG,	ΚP,	KR,	KZ	, LC,	LK,	LR,	LT,	LV,	MD,	MG,
		MK,	MN,	MW,	MX,	NO,	NZ,	PL,	RO,	RU	, SD,	SG,	SI,	SK,	SL,	TJ,	TM,
		TR,	TT,	UA,	ŪĠ,	US,	UΖ,	VN,	ΥU,	ZW							
	RW:	GH,	KE,	LS,	MW,	SD,	SZ,	UG,	ZW,	BF	, BJ,	CF,	CG,	CI,	CM,	GΑ,	GN,
		ML,	MR,	NE,	SN,	TD,	TG					.,					
ΕP	8266	82			A1		1998	0304		EP :	1997-	3064	26		1	9970	822
ΕP	8266	82			B1	:	2003	0312									
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT,	LI,	LU,	NL,	SE,	MC,	PT,
		ΙE,	SI,	LT,	LV,	FI,	RO										
CA	2263	175			- A1		1998	0305		CA :	1997-	2263	175		1	9970	822
AU	9742	335		t	Α		1998	0319	٠.	AU :	1997-	4233	5		1	9970	
ΑU	7239	87		•	B2	:	2000	0907									
IN	1829	40			A1	:	1999	0814		IN :	1997-	CA15	49		. 1	9970	822
BR	9713	176			Α	:	2000	0208		BR :	1997-	1317	6		1	9970	822
CN	1244	124			Α	:	2000	0209	1	CN :	1997-	1974	34		1	9970	822
	2000				A2	:	2001	0628		HU :	2'000-	1172			1	9970	822
HU	2000	0117	2		A3	:	2002	0128									
	3338	39	,		Α	:	2001	0629	]	NZ :	1997-	3338	39		1	9970	822
IL	1286	41			Α	:		1031			1997-						
	9900				T2	:	2002	0121	'	TR .	1999-	403			1	9970	822
JP	2002	5141						0514			1998-	_				9970	
ΑT	2342	95			$\mathbf{T}$	:	2003	0315		AT :	1997-	3064	26		1	9970	822

19970822 ES 2195089 Т3 20031201 ES 1997-306426 19970825 ZA 9707617 19990225 ZA 1997-7617 Δ 19970825 US 6713494 B1 20040330 US 1997-918741 19990225 NO 1999-914 19990225 NO 9900914 Α 20000626 KR 1999-701682 19990227 KR 2000035941 Α US 1996-24831P P 19960828 PRIORITY APPLN. INFO.: W 19970822 WO 1997-US14768

OTHER SOURCE(S): MARPAT 128:221639

AB A method for prepg. an amorphous form of a benzothiophene such as raloxifene is described. Thus, raloxifene-HCl was prepared by a series of reactions starting from 3-methoxybenzenethiol and 4'-methoxyphenacyl bromide. A formulation contained PEG-1450 70, spray-dried lactose 1.5, colloidal SiO2 1.5, Polysorbate-80 2.0, and raloxifene-HCl 25%. The bioavailability of raloxifene-HCl and the pharmacol. effects of this compound on osteoporosis and hyperlipidemia were determined

REFERENCE COUNT:

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1997:589698 CAPLUS Full-text

1

DOCUMENT NUMBER:

127:272904

TITLE:

Evaluation of piperidinoethoxy moiety as an antiestrogenic substituent in non-steroidal

anti-estrogens: fertility regulation

AUTHOR (S):

Tripathi, Sachi; Dwivedy, Indra; Dhar, J. D.; Dwivedy,

Anila; Ray, Suprabhat

CORPORATE SOURCE:

Medicinal Chemistry Division, Central Drug Research

Institute, Lucknow, 226 001, India

SOURCE:

Bioorganic & Medicinal Chemistry Letters (1997),

7(16), 2131-2136

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER:
DOCUMENT TYPE:

Elsevier Journal

LANGUAGE:

English

AB A piperidinoethoxy substituent in non-steroidal antiestrogens has a relatively higher antiestrogenic effect as compared to a pyrrolidinoethoxy moiety. However, the antagonistic activity is more depended on the mol. geometry than the nature of the basic chain. No significant difference in the antifertility activity in these two sets of compds. was observed

REFERENCE COUNT:

12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1997:124440 CAPLUS Full-text

DOCUMENT NUMBER:

126:144105

TITLE:

Preparation of 3-phenylbenzo[b]thiophenes

INVENTOR(S):

Hoard, David W.; Luke, Wayne D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA; Hoard, David W.; Luke, Wayne

D.

SOURCE:

PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

r: 1

PATENT NO.	KIND DATE	APPLICATION NO.	DATE
WO 9640677	A1 19961219	WO 1996-US9477	19960604
W: AL, AM, AT,	AU, AZ, BB, BG,	BR, BY, CA, CH, CN, CZ,	DE, DK, EE,

```
ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS,
             LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
             SE, SG
         RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
             IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA
                                 19970225
                                             US 1995-481015
     US 5606075
                          Α
                                                                     19950607
                                             CA 1996-2223709
                                                                     19960604
     CA 2223709
                          A1
                                 19961219
                                             AU 1996-61010
     AU 9661010
                          Α
                                 19961230
                                                                     19960604
     AU 703017
                                 19990311
                          B2
     EP 830355
                          A1
                                 19980325
                                             EP 1996-918320
                                                                     19960604
             AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
             SI, LT, LV, FI
     CN 1192738
                          Α
                                 19980909
                                             CN 1996-196109
                                                                     19960604
     BR 9608851
                          Α
                                 19990608
                                             BR 1996-8851
                                                                     19960604
     JP 11507347
                          T
                                 19990629
                                             JP 1996-501787
                                                                     19960604
     HU 9900898
                                 19990728
                                             HU 1999-898
                                                                     19960604
                          A2
     HU 9900898
                          A3
                                 20000228
                                             EP 2000-128207
                                                                     19960604
     EP 1092714
                          A2
                                 20010418
     EP 1092714
                          A3
                                 20010704
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
             SI, LT, LV, FI
                                             IL 1996-122128
     IL 122128
                          Α
                                 20010808
                                                                     19960604
     NO 9705627
                          Α
                                 19980127
                                             NO 1997-5627
                                                                     19971204
PRIORITY APPLN. INFO.:
                                             US 1995-481015
                                                                     19950607
                                                                  Α
                                             EP 1996-918320
                                                                  A3 19960604
                                             WO 1996-US9477
                                                                  W
                                                                     19960604
OTHER SOURCE(S):
                         MARPAT 126:144105
```

$$R^{1}$$
  $R^{2}$ 

GI

L3

AB Title compds. [I; R1, R2 = H, halo, (aryl)alkoxy, NH2] were pred. by cyclization of 4-R1C6H4CH:C(SR4)C6H4R2-4 [R4 = trialkylsilyloxy, (di)(alkyl)amino, alkylthio, etc.] in the presence of an acid.

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CAPLUS COPYRIGHT 2007 ACS on STN
     ANSWER 24 OF 38
ACCESSION NUMBER:
                         1996:740256 CAPLUS Full-text
DOCUMENT NUMBER:
                         126:7985
                         Preparation of 3-[4-(2-heterocyclylethoxy)benzoyl-2-
TITLE:
                         phenylbenzothiophenes for use in alleviating the
                         symptoms of post-menopausal syndrome
                         Dodge, Jeffrey Alan; Jones, Charles David; Bourgeois,
INVENTOR(S):
                         Tokarz Michelle Lee
PATENT ASSIGNEE(S):
                         Eli Lilly and Co., USA
SOURCE:
                         Eur. Pat. Appl., 67 pp.
                         CODEN: EPXXDW
DOCUMENT TYPE:
                         Patent
```

LANGUAGE: English

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

> PATENT NO. KIND DATE APPLICATION NO. DATE

EP 738725 A2 19961023 EP 1996-302713 19960418 EP 738725 A3 19970305 R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, NL, PT, SE US 6608090 В1 20030819 US 1995-426552 19950421 CA 2215902 CA 1996-2215902 19960418 A1 19961024 WO 1996-US5382 19960418 WO 9632937 **A1** 19961024 AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG AU 9655549 Α 19961107 AU 1996-55549 19960418 Т 19960418 JP 11504013 19990406 JP 1996-531911 PRIORITY APPLN. INFO.: US 1995-426339 19950421 US 1995-426552 19950421 19960418 WO 1996-US5382

OTHER SOURCE(S):

MARPAT 126:7985

GI

$$R^{1}$$
 $R^{2}$ 
 $R^{2$ 

AB The title compds. [I; R1, R2 = H, OH, alkoxy, etc.; R3 = (substituted) pyrrolidino, piperidino, piperazino, etc.], useful in alleviating the symptoms of post-menopausal syndrome related to osteoporosis, cardiovascular disease, hyperlipidemia, estrogen-dependent cancer, and in alleviating the symptoms of uterine fibroid disease, endometriosis, aortal smooth muscle cell proliferation, and restenosis, were prepared and formulated. Thus, reaction of bromide II with 3-phenylpyrrolidine in DMF followed by demethylation with EtSH/AlCl3 in CH2Cl2 afforded I [R1, R2 = H; R3 = 3-Ph-pyrrolidin-1-yl] which reduced 63.4% serum cholesterol at 10 mg/kg.

ANSWER 25 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER:

DOCUMENT NUMBER:

1996:672963 CAPLUS Full-text

126:7983

TITLE:

Process for the synthesis of benzo[b] thiophenes

INVENTOR (S):

Hoard, David W.; Luke, Wayne D.

PATENT ASSIGNEE(S):

Eli Lillŷ and Company, USA

SOURCE:

U.S., 10 pp.

CODEN: USXXAM

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA	rent i	. O <i>v</i>			KIN	D .	DATE			API	LI	CAT	ION I	NO.		1	DATE	
·us	5569	772		,	Α		1996	1029		US	19	95-4	4868	73			19950	607
	2223																	
WO	9640	578			<b>A</b> 1		1996	1219		WO	19	96-1	US93!	57			19960	604
							BB,											
							ΙL,											
							MK,				-						-	
			SG	,	•	•	•	•	•		•	•	•	•	•			
	RW:	•		MW.	SD,	SZ.	UG,	AT,	BE,	CH	I.	DE.	DK.	ES.	FI.	FR	GB.	GR.
							PT,											•
AU	9660			•	•	•	•	•	•		•	•	•		•			604
	6985						1998											•
EP	8303	56			<b>A</b> 1		1998	0325		EΡ	19	96-9	9182	77			19960	604
	8303																	
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	٤,	IT,	LI,	LU,	NL,	SE	PT,	IE,
		SI,	LT,	LV,	FI							•						
CN	11922	212			Α		1998	0902		CN	19	96-	19589	99		:	L9960	604
	96093																	
JP	1150	7338			T		1999											
HU	99009	903			A2		1999	0728		HU	19	99-9	903			:	19960	604
HU	99009	903					2001	0129										
IL	12209	91			Α		2001	0520		IL.	19	96-3	1220	91		-	19960	604
AT	12209 2045	75			T		2001	0915		AΤ	19	96-9	9182	77		-	L9960	604
ES	21597	742			Т3		2001	1016		ES	19	96-9	9182	77		:	L9960	604
PT	83035	56			T		2001	1228		PT	19	96-9	9182	77		:	19960	604
NO	97055	579															19971	203
PRIORITY	APPI	LN.	INFO	. :						US	19	95-4	1868	73	7	Α :	19950	607
									1	WO	19	96-t	JS935	57	1	W 1	19960	604
OTHER SO	URCE	(S):			CASI	REAC	T 12	6:798	33;	MAR	PA	T 12	26:79	983				
GI																		

$$R^{1}$$
 $R^{2}$ 
 $R^{2}$ 

The title compds. I [R1, R2 = H, alkoxy, etc.] are prepd. Thus, treatment of (E)-tert-Bu 4,4'-dimethoxystilbenyl sulfoxide with p-toluenesulfonic acid in refluxing toluene gave, after workup and purifn, (E)- and (Z)-I [R1 = R2 = MeO].

L3 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:649600 CAPLUS Full-text

DOCUMENT NUMBER: 125:266032

TITLE: Phosphorous-containing benzothiophenes, their

preparation, their use in treating postmenopausal

syndrome-associated indications and estrogen-dependent

diseases, and pharmaceuticals containing them

INVENTOR(S): Bryant, Henry U.; Dodge, Jeffrey A.; Nissen, Jeffrey

s.

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: Eur. Pat. Appl., 19 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 729964	A1	19960904	EP 1996-300878	19960209
EP 729964	B1	20010509		
R: AT, BE, CH,	DE, DK	, ES, FR, GB	, GR, IE, IT, LI, LU,	NL, PT, SE
US 6479517	B1	20021112	US 1995-395944	19950228
ES 2158242	Т3	20010901	ES 1996-300878	19960209
CA 2169414	A1	19960829	CA 1996-2169414	19960213
JP 08259560	Α	19961008	JP 1996-25281	19960213
US 5998443	A	19991207	US 1997-946842	19971008
PRIORITY APPLN. INFO.:			US 1995-395944	A 19950228
OTHER SOURCE(S):	MARPAT	125:266032		
GT				

Phosphorus-contg. benzothiophene compds. I [R1, R2 = H, OH, halo, OPO(0-alkyl)2, OPO(0-aryl)2, OPO(alkyl)2, OPO(aryl)2, OPO3-2, in which not more than one of R1 and R2 may be H, OH or halo; R3, R4 = CO(CH2)3, CO(CH2)4, alkyl, or R3 and R4 combine to form, with the nitrogen to which they are attached, piperidine, morpholine, pyrrolidine, 3-methylpyrrolidine, 3,3-dimethylpyrrolidine, 3,4-dimethylpyrrolidine, azepine, or pipecoline], and pharmaceutically acceptable salts thereof, are provided which are useful for the treatment of the various medical indications associated with postmenopausal syndrome, as well as estrogen-dependent diseases, including cancer of the breast, uterus and cervix. Also provided are intermediate compds. and processes useful for preparing the pharmaceutically active compds.

of the invention, as well as pharmaceutical compns. containing compds. of the invention.

ANSWER 27 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:333087 CAPLUS Full-text

DOCUMENT NUMBER:

125:86485

TITLE:

Prepn. of vinyl sulfenic acid derivatives for

benzo[b] thiophene synthesis

INVENTOR(S):

Hoard, David W.; Luke, Wayne D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 13 pp. CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	TENT						DATE			API	PLICA	CION	NO.		D	ATE	
						-									-		<b></b> .
US	55:14	826			A		1996	0507		US	1995	-4836	07		1	9950	607
CA	2224	225 -			<b>A</b> 1		1996	1219		CA	1996	-2224	225		1	9960	604
	9640																
	W:	AL,	AM,	AT,	AU,	AZ	BB,	BG,	BR,	В	, CA	CH,	CN,	CZ,	DE,	DK,	ΕE,
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											NO.						
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	RW:	•		MW.	SD.	S7.	IIG.	ΔТ.	BE.	CF	I. DE.	DK.	ES.	FT.	FR.	GB.	GR.
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	6980										1000	0100	_		_	,,	•••
	8303									БD	1996.	. 91 8 3	14		1	9960	604
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										CN	1996-	-1353	4 /		1	9900	004
	1068	-					2001								_		
BR	9608	847			A						1996-					9960	
	1150						1999				1997-					9960	
HU	9900	923			A2		1999	0728		HU	1999-	-923			1	9960	604
	9900						2000	0228			•						
	1221						2001	0520		ΪL	1996-	-1221	27		1	9960	604
NO	9705	633 .			Α		1998	0128		NO	1997-	-5633			1	9971	204
	1330						2002	0109		CN	2000-	-1307	96		2	0001	212
PRIORIT	Y APP	LN.	INFO	. :						US	1995-	4826	92		A 1	9950	607
											1995-						
	•								,	WO	1996-	-US94	60	1	W 1	9960	604
CT																	

GI

$$R^1$$
 CH  $=$   $CH$   $=$   $CH$   $=$   $R^2$ 

The present invention is directed to novel vinyl sulfenic acid derivs. I [R1, AB R2 = H, alkoxy, arylalkoxy, halo, amino; R4 = OSi(R3)3, NR5R6, SR8; R5and/or R6 = H, alkyl, arylalkyl, aryl, -(CH2)5-, -(CH2)4-, -(CH2)20(CH2)2-, -(CH2)6-; R8 = alkyl, aryl, arylalky] useful for the synthesis of benzo[b]thiophenes, in particular 2-arylbenzo[b]thiophenes. E.g., desoxyanisoin reacts with 2-methyl-2-propanethiol to give I [R1 = R2 = OMe; R4 = C(Me)3] which in turn cyclizes to 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene.

L3 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:256454 CAPLUS Full-text

DOCUMENT NUMBER:

124:289252

TITLE:

Process for preparing benzoic acid derivative

intermediates and benzothiophene pharmaceutical agents

INVENTOR(S):
PATENT ASSIGNEE(S):

Kjell, Douglas Patton Eli Lilly and Co., USA

COLLEGE

Eur. Pat. Appl., 16 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 699673	A1	19960306	EP 1995-306053	19950830
EP 699673	B1	19980422		•
R: AT, BE, CH,	DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU,	, NL, PT, SE
US 5731436	Α	19980324	US 1994-298891	19940831
IL 115091	A	20000831	IL 1995-115091	19950828
IL 126593	Α	20000831	IL 1995-126593	19950828
CA 2157235	<b>A1</b>	19960301	CA 1995-2157235	19950830
FI 9504068	Α	19960301	FI 1995-4068	19950830
HU 73136	A2	19960628	HU 1995-2539	19950830
BR 9503847	Α	19960917	BR 1995-3847	19950830
AT 165356	T	19980515	AT 1995-306053	19950830
ES 2114722	T3	19980601	ES 1995-306053	19950830
JP 08119912	Α	19960514	JP 1995-223184	19950831
US 5955608	A	19990921	US 1998-16761	19980130
PRIORITY APPLN. INFO.:			US 1994-298891	A 19940831
•			IL 1995-115091	A3 19950828
OTHER SOURCE(S)	маррат	124 - 28925	2	

OTHER SOURCE(S):

MARPAT 124:289252

GI

$$O(CH_2)$$
  $nNR1R2$ 
 $O(CH_2)$   $nNR1R2$ 
 $OR4$ 
 $R^3O$ 
 $OR4$ 
 $II$ 

AB The present invention provides a novel process for prepg. a compd. of formula RO2C(p-C6H4)O(CH2)nNR1R2 [R = C1-C4 alkyl; R1, R2 = C1-C4 alkyl, or combine to form piperidinyl, pyrrolidinyl, methylpyrrolidino, dimethylpyrrolidino,

morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; n = 2, 3; or a pharmaceutically acceptable salt thereof, comprising (a) condensing (C1-C4 alkyl) 4-hydroxybenzoate with ethylene carbonate or propylene carbonate in the presence of a condensation catalyst and a moderately polar, water immiscible solvent having a high b.p.; (b) reacting the product of step (a), a compound of formula RO2(p-C6H4)O(CH2)nOH [R and n are as defined above, with a leaving group donor]; and (c) reacting the product of step (b), a compound of formula RO2(p-C6H4)O(CH2)nX [R and n are as defined above; X = leaving group with a base selected from the group consisting of piperidine, pyrrolidine, methylpyrrolidine, dimethylpyrrolidine, morpholine, dimethylamine, diethylamine, and 1-hexamethyleneamine]. The product of the above process also is novel and is useful for the preparation of pharmaceutically active compds. of formula I, particularly via the following novel process [R = C1-C4 alkyl; R1 and R2 each are independently C1-C4 alkyl, or combine to form piperidinyl, pyrrolidinyl, methylpyrrolidino, dimethylpyrrolidino, morpholino, dimethylamino, diethylamino, of 1-hexamethyleneimino; n = 2, 3; or a pharmaceutically acceptable salt thereof, comprising (a) condensing (C1-C4 alkyl) 4-hydroxybenzoate with ethylene carbonate or propylene carbonate in the presence of a condensation catalyst and a moderately polar, water immiscible solvent having a high b.p.; (b) reacting the product of step (a), a compound of formula RO2C(p-C6H4)O(CH2)nOH [R and n are as defined above, with the leaving group donor]; (c) reacting the product of step (b), a compound of formula RO2C(p-C6H4)O(CH2)nX [R and n are as defined above; X = leaving group with a base selected from the group consisting of piperidine, pyrrolidine, methylpyrrolidine, dimethylpyrrolidine, morpholine, dimethylamine, diethylamine, and 1-hexamethyleneimine]; (d) reacting the product of step (c) with a compound of formula II [R3 and R4 are as defined above], or a pharmaceutically acceptable salt thereof; (e) optionally removing the reaction product from step (d); and (f) optionally forming a salt of the reaction product from either step (d) or step (e).

ANSWER 29 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3 ACCESSION NUMBER:

1996:237478 CAPLUS Full-text

DOCUMENT NUMBER:

124:289249

TITLE:

An improved process for preparing 3-(4aminoethoxybenzoyl) benzo[b] thiophenes

INVENTOR (S):

Alt, Charles Arthur Eli Lilly and Co., USA

PATENT ASSIGNEE(S): SOURCE:

Eur. Pat. Appl., 15 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PAT	TENT NO.			KIN	)	DATE		API	PLICAT	ION I	NO.		D	ATE	
	- <b></b>				-										
EP	693488			<b>A1</b>		1996	0124	EP	1995-	3050	85		19	950	720
ΕP	693488			B1		2001	0919								
	R: AT,	BE,	CH,	DE,	DK	, ES,	FR,	GB, GE	R, IE,	IT,	LI,	LU,	NL,	PT,	SE
US	5523416			Α		1996	0604	US	1995-	4222	94		19	950	414
HU	71596			A2		1996	0129	HU	1995-	2176			19	950	719
AU	9525068			Α		1996	0201	AU	1995-	2506	8		19	950	719
ΑU	684181			B2		1997	1204								
ZA	9506031			Α		1997	0120	ZA	1995-	6031			19	950	719
CA	2154319			A1		1996	0123	CA	1995-	2154	319		19	950	720
FI	9503513			Α		1996	0123	FI	1995-	3513			19	950	720
NO	9502891			Α		1996	0123	NO	1995-	2891			19	950	720
CN	.1116624			Α		1996	0214	CN	1995-	1096	18		19	950	720

JP 08053440	` A	19960227	JP 1995-183923		19950720
IL 114684	Α	19990620	IL 1995-114684		19950720
AT 205842	T	20011015	AT 1995-305085		19950720
· ES 2160668	<b>T</b> 3	20011116	ES 1995-305085		19950720
PT 693488	T	20020228	PT 1995-305085		19950720
BR 9503408	A	19960227	BR 1995-3408		19950721
US 5512684	A	19960430	US 1995-512724		19950808
PRIORITY APPLN. INFO.:			US 1994-279456	Α	19940722
			US 1995-422294	A1	19950414

OTHER SOURCE(S):

CASREACT 124:289249; MARPAT 124:289249

GI

A process for prepg. 6-alkoxy-3-(4-alkoxyphenyl)benzo[b]thiophenes (I; A = H; AB R = same or different C1-6 alkyl) in good yield on a manufacturing scale without generating a thick, potentially yield-reducing, paste and thereby without mixing problems, involves intramol. cyclization of  $\alpha$ -(3alkoxyphenylthio) -4-alkoxyacetophenones (II; R = same as above). invention also provides methods for converting  $\alpha$ -(alkoxyphenylthio)-4alkoxyacetophenones I (A = H; R = same as above) into 6-hydroxy-2-(4hydroxyphenyl) -3-[4-(2- aminoethoxy)benzoyl]benzo[B]thiophenes I (A = Q, R = H; R5 = NR1R2; wherein R1, R2 = C1-4 alkyl, or R1R2 = C4-6 polymethylene or CH2CH2OCH2CH2) via acylation of a dialkoxy benzo[b] thiophene I (A = H; R = same as above) with an acylating agent R4-Q (R4 = C1, Br, an active ester, etc.; R5 = same as above) under Friedel-Crafts conditions. Thus, 164 g  $\alpha$ bromo-4-methoxyacetophenone was added portion-wise to a mixture of 100 g 4methoxybenzenethiol and 39 g KOH in 300 mL and denatured EtOH in a cooling and stirred for 10 min in the cooling bath and at ambient temperature for 3 h to give, after workup, 158 g  $\alpha$ -(3-methoxyphenylthio)-4- methoxyacetophenone. The latter compound (6.92 g) was added steadily over 1/2 h to a mixture of 41.5 g polyphosphoric acid and 13.8 g phosphoric acid and the reaction mixture was heated at 85° for 1.75 h and cooled to 50°, to give , after extraction with toluene and crystallization, the desired 6-isomer, I (A = H, R = Me) (69% yield). The latter compound (30 g) was heated with 90 g pyridine hydrochloride with stirring at 210° for 30 min to give, after workup, 25.5 g I (A = R = H), which (40 g) was acetylated by Ac20 in the presence of 4dimethylaminopyridine in pyridine to give 52.5 g I (A = H, R = Ac). This compound (20 g) was added to a solution of 4-(2-piperidinoethoxy)benzoyl chloride (prepared from 16.3 g of the benzoic acid derivative) in ClCH2CH2Cl and stirred vigorously, followed by adding 73.4 g AlCl3 over 3 min, and the resulting mixture was stirred for 1 h to give, after workup, the desired product I [A = Q (wherein R5 = piperidino), R = Ac] as an oil, which was saponified with a mixture of 275 mL MeOH and 55 mL 5 n aqueous NaOH under reflux to give 10.5 g the title compound I [A = Q, wherein R5 = piperidino, R = H].

ANSWER 30 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3

1996:150242 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER:

124:202950

Preparation of benzothiophene glucopyranosides as TITLE:

antihyperlipidemics.

Dodge, Jeffrey Alan; Frolik, Charles Alan; Lindstrom, INVENTOR(S):

Terry Donald; Lugar, Charles Willis Iii; Staten,

Gilbert Stanley

Eli Lilly and Co., USA PATENT ASSIGNEE(S):

SOURCE: Eur. Pat. Appl., 20 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
			EP 1995-303265	19950516
EP 683170	B1	19990922		
R: AT, BE, CH,	DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU,	NL, PT, SE
US 5567820	Α	19961022	US 1995-404701	19950315
US 6723739		20040420	US 1995-405555	
CA 2149501	A1	19951121	CA 1995-2149501	19950516
ZA 9503975	Α	19961118	ZA 1995-3975	19950516
AT 184880	T	19991015	AT 1995-303265	19950516
ES 2136799	T T3	19991201	ES 1995-303265	19950516
AU 9520121	Α	19951130	AU 1995-20121	19950517
AU 683734		19971120		
JP 07316180	A	19951205	JP 1995-118338	19950517
FI 9502420	A	19951121	FI 1995-2420	19950518
NO 9501954	A	19951121	NO 1995-1954	19950518
NO 304686		19990201		
CN 1116626	Α	19960214	CN 1995-106322	19950518
CN 1039013	В	19980708		
BR 9502079	A	19960305	BR 1995-2079	19950518
HU 73788	A2	19960930	HU 1995-1466	19950518
HU 219335	В	20010328		
IL 113780	Α	19990620	IL 1995-113780	19950518
GR 3032142	Т3		GR 1999-403228	19991215
	A1	20040826	US 2004-778865	20040212
PRIORITY APPLN. INFO.:			US 1994-246655	
•			US 1995-405555	A1 19950315

OTHER SOURCE(S):

CASREACT 124:202950

GI

AB Raloxifene metabolites (I) and (II) and their hydrochloride salts were prepared Thus, I and II, prepared from 6-tert-butyldimethylsilylraloxifene and 4'-tert-butyldimethylsilylraloxifene and Me 1,2,3,4-O-tetraacetyl-D-glucopyranuronate, at 1.3 mg/kg in rats decreased serum cholesterol by 44.5% and 56.8%, resp. Drug formulations are given.

L3 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:123714 CAPLUS Full-text

DOCUMENT NUMBER:

124:155994

TITLE:

Pharmaceutical compositions containing

2-phenyl-3-aryoylbenzothiophenes for for inhibiting

Ι

bone loss and lowering serum cholesterol

INVENTOR(S):

Draper, Michael W.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Can. Pat. Appl., 31 pp.

CODEN: CPXXEB

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2141999	A1	19950903	CA 1995-2141999	19950207
US 5478847	A	19951226	US 1994-205012	19940302
ZA 9500976 '	A	19960807	ZA 1995-976	19950207
NZ 314699	A	20000728	NZ 1995-314699	19950207
EP 674903	A1	19951004	EP 1995-300842	19950210
R: AT, BE, CH,	DE, DK	, ES, FR, C	GB, GR, IE, IT, LI, LU,	NL, PT, SE
NO 9500774	A	19950904	NO 1995-774	19950228
RU 2100024	C1	19971227	RU 1995-102778	19950228
RU 2150275	C1	20000610	RU 1996-119781	19950228
AU 9513551	Α	19950907	AU 1995-13551	19950301
AU 702575	B2	19990225		
JP 07267861	Α	19951017	JP 1995-41769	19950301
JP 2818384	B2	19981030		
BR 9500784	Α	19951024	BR 1995-784	19950301
CN 1119530	Α	19960403	CN 1995-100021	19950301

HU 72638	A2	19960528	HU	1995-634		19950301
JP 10291932	Α	19981104	JP	1998-107550		19950301
JP 10310525	Α	19981124	JP	1998-107549		19950301
US 5610168	Α	19970311	US	1995-422289		19950414
US 5641790	. <b>A</b>	19970624	US	1995-422417		19950414
US 5747510	Α	19980505	US	1997-788984		19970127
US 39050	E1	20060328	US	2003-375274		20030227
PRIORITY APPLN. INFO.:		•	US	1994-205012	Α	19940302
			JP	1995-41769	A3	19950301
			US	1995-422417	A1	19950414

AB A method of inhibiting bone loss or resorption, or lowering serum cholesterol, comprises administering to a human in need thereof pharmaceutical compns. containing 2-phenyl-3-aryoylbenzothiophenes, salt or solvate thereof, in a low dosage amount Raloxifene (I) at 50-200 mg decreased LDL cholesterol in postmenopausal women and there was no changes in HDL cholesterol level. A capsule contained I 150, starch 150, starch flowable powder 397, and silicone fluid 350 3.0 mg.

L3 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1995:991025 CAPLUS Full-text

DOCUMENT NUMBER:

124:106673

TITLE:

Methods for lowering serum cholesterol

INVENTOR (S):

Black, Larry J.; Bryant, Henry U.; Cullinan, George

J.; Kauffman, Raymond F.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 14 pp. Cont.-in-part of U.S. Ser. No. 995, 222,

abandoned.
CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5464845	A	19951107	US 1993-159159	19931130
TW 383306	В	20000301	TW 1993-82100751	19930204
RU 2123335	C1	19981220	RU 1993-55026	19931213
ZA 9309427	Α	19950615	ZA 1993-9427	19931215
SK 279271	В6	19980805	SK`1993-1421	19931215
IL 108042	A	19980104	IL 1993-108042	19931216
CZ 283863	B6	19980617	CZ 1993-2790	19931216
HU 69686	A2	19950928	HU 1993-3676	19931220
HU 223342	B1	20040628	•	
RO 113806	B1	19981130	RO 1993-1739	19931220
PL 177349	B1	19991029	PL 1993-301579	19931220
CA 2112017	<b>A1</b>	19940623	CA 1993-2112017	19931221
CA 2112017	C	20050614		
NO 9304740	Α	19940623	NO 1993-4740	19931221
AU 9352578	Α	19940707	AU 1993-52578	19931221
AU 669235	B2	19960530		
BR 9305182	Α	19940816	BR 1993-5182	19931221
JP 06234632	Α	19940823	JP 1993-323825	19931222
JP 3197129	B2	20010813		
CN 1094042	Α	19941026	CN 1993-121277	19931222
CN 1043608	В	19990616		
AT 233559	T	20030315	AT 1993-310438	19931222
ES 2193142	Т3	20031101	ES 1993-310438	19931222
PRIORITY APPLN. INFO.:	•	•	US 1992-995222	B2 19921222

GI

$$\begin{array}{c|c} & \text{CO} & \text{OCH}_2\text{CH}_2\text{(CH}_2\text{)}_n\text{R}^2 \\ \\ \text{R}^1 & \text{S} & \text{CO} & \text{CO} \end{array}$$

AB A method of lowering serum cholesterol levels comprising administering to a patient a serum cholesterol lowering amount of a compound I wherein n is 0, 1 or 2; R is hydroxyl, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R1 is hydrogen, hydroxyl, chloro, bromo, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R2 is a heterocyclic ring (pyrrolidino, piperidino, or hexamethyleneimino); or a pharmaceutically acceptable salt or solvate thereof. The tested compds. lowered LDL without significantly affecting primary sex targets.

L3 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1995:362913 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

122:213884

TITLE:

A chemical probe for the estrogen receptor: synthesis

of the 3H-isotopomer of raloxifene

AUTHOR (S):

Dodge, Jeffrey A.; Stocksdale, Mark G.; Jones, C.

David

CORPORATE SOURCE:

Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE:

Journal of Labelled Compounds & Radiopharmaceuticals

(1995), 36(1), 43-9

CODEN: JLCRD4; ISSN: 0362-4803

PUBLISHER:
DOCUMENT TYPE:

Wiley Journal

LANGUAGE:

English

AB Radiolabeled raloxifene (LY156758) was prepd. by tritium gas hydrogenolysis of a 3-aroyl bis-brominated precursor. The requisite halogenated intermediate was accessed by regioselective aroylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene with 3,5-dibromo-4-[2-(1-

piperdinyl)ethoxy]benzoyl chloride. Selective deprotection of the aryl Me ethers in the presence of the ethoxy side-chain followed by palladium catalyzed halogen-tritum exchange provided the target compound with a specific activity of 30.1 Ci/mmol.

L3 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1994:700754 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

121:300754

TITLE:

[[(Alkylsulfonyl)oxy]benzo[b]thienyl]methanones and

[[(aminocarbonyl)oxy]benzo[b]thienyl]methanones

pharmaceuticals

INVENTOR(S):

Black, Larry John; Bryant, Henry Uhlman; Cullinan,

George Joseph

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 26 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 617030	7.1	10040020	EP 1994-301871	19940316
		19990526	BF 1994 3010/1	17740310
	B1		un on the two it its	NI DT CE
			B, GR, IE, IT, LI, LU,	
US 5482949			US 1993-35121	
	Α			
CA 2119091		19940920	CA 1994-2119091	
NO 9400940	A	19940920	NO 1994-940	19940316
AU 9457863	A	19940922	AU 1994-57863	19940316
AU 670177	B2	19960704		
BR 9401183	Α	19941101	BR 1994-1183	19940316
HU 70549	A2	19951030	HU 1994-774	19940316
AT 180479	T	19990615	AT 1994-301871	19940316
ES 2132339	<b>T</b> 3	19990816	ES 1994-301871	19940316
FI 9401262	Α	19940920	FI 1994-1262	19940317
JP 06321937	A	19941122	JP 1994-47091	19940317
CN 1097420	A	19950118	CN 1994-102910	
US 5994371	A	19991130		
US 5599833	A	19970204	US 1996-588670	
US 5605924		19970225		
	A	19980825	US 1997-958535	
US 5798351	A	19900025		
PRIORITY APPLN. INFO.:			US 1993-35121	
				A3 19950222
OTHER SOURCE(S):	MARPAT	121:300754	<b>:</b> ,	

The (4-alkoxybenzoyl)benzo[b]thiophene-6-sulfonates and (4-alkoxybenzoyl)benzo[b]thien-6-yl carbamates I (R = OH, alkoxysulfonyl, carbamoyl; R1 = H, OH, halo, etc.; R2 = pyrrolidino, piperidino, etc.; X = bond, methine) were disclosed as agents for inhibiting the loss of bone, lowering serum cholesterol levels and therapeutically treating hormone dependent mammalian breast and uterine carcinoma. A specifically claimed example compound is [6-[(pentylsulfonyl)oxy]-2-[4-[(pentylsulfonyl)oxy]phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (II).

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

L3 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1984:448784 CAPLUS Full-text

DOCUMENT NUMBER:

101:48784

TITLE:

GI

Antiestrogens. 2. Structure-activity studies in a series of 3-aroyl-2-arylbenzo[b]thiophene derivatives leading to [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride (LY 156758), a remarkably effective estrogen antagonist with only minimal intrinsic estrogenicity

escrogenici

AUTHOR(S): Jones, Charles D.; Jevnikar, Mary G.; Pike, Andrew J.;

Peters, Mary K.; Black, Larry J.; Thompson, Allen R.;

Falcone, Julie F.; Clemens, James A.

CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE: Journal of Medicinal Chemistry (1984), 27(8), 1057-66

CODEN: JMCMAR; ISSN: 0022-2623

Ι

DOCUMENT TYPE:

Journal

LANGUAGE:

English

GΙ

In an effort to prep. nonsteroidal antiestrogens demonstrating greater AB antagonism and less intrinsic estrogenicity than those currently available, a series of 3-aroyl-2-arylbenzo[b]thiophene derivs. was synthesized. These compds. were prepared by Friedel-Crafts aroylation of appropriate O-protected 2-arylbenzo[b]thiophene nuclei with basic side-chain-bearing benzoyl chlorides followed by removal of the protective groups to provide the desired compds. containing both hydroxyl and basic side-chain functionality. A particularly useful method for the cleavage of aryl methoxy ethers without removal of (dialkylamino) ethoxy side chain functionality elsewhere in the mol. was AlCl3/EtSH. The benzothiophene derivs. were tested for their ability to inhibit the growth-stimulating action of estradiol on the immature rat uterus. Seemingly minor changes in the side-chain amine moiety had profound effects on the ability of the compds. to antagonize estradiol. Analogs having basic side chains containing cyclic (pyrrolidine, piperidine, and hexamethyleneamine) moieties had less intrinsic estrogenicity and antagonized estradiol action more completely than their noncyclic counterparts. The most effective antiestrogen in the series, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (I) [84449-90-1], elicited a modest uterotropic activity that did not increase with increasing dose. In antagonism of estradiol, I exhibited a degree of inhibition surpassing that of tamoxifen at any dose tested. The new benzothiophene antiestrogen also had high affinity for rat uterine cytoplasmic estrogen receptor and was an inhibitor of the growth of DMBA-induced rat mammary tumors.

L3 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1984:156501 CAPLUS Full-text

DOCUMENT NUMBER: 100:156501

TITLE: Antiestrogenic and antiandrogenic benzothiophenes

INVENTOR(S): Jones, Charles D.

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: U.S., 23 pp. Cont.-in-part of U.S. Ser. No. 246,335,

abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 4418068	Α	19831129	US 1981-331042		19811216
ZA 8202247	A	19831130	ZA 1982-2247		19820401
PRIORITY APPLN. INFO.:			US 1981-246335	A2	19810403
OTHER SOURCE(S):	CASREA	CT 100:15650	)1		
GI		· ·			•

AB Antiandrogenic and antiestrogenic [(piperidinoethoxy)benzoyl]benzothiophen es I [R,R1 = H, R2CO; R2 = H, cycloalkyl, (un)substituted alkyl, Ph] were prepared Thus, 2-(4-hydroxyphenyl)benzo[b]thiophene-6-ol was esterified with MeSO2Cl and the diester subjected to Friedel-Crafts acylation with 4-(2-piperidinoethoxy)benzoyl chloride to give I (R = R1 = MeSO2). This was saponified to give I (R = R1 = H) (II). Immature female rats administered 0.03 µg estradiol propionate (III) s.c. together with 3 mg II s.c. daily for 4 d had average uterus weight of 21.3 mg. Those given III alone had average uterus weight of 65.9 mg. I also were effective as antiandrogens and as mammary tumor inhibitors.

L3 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1983:71917 CAPLUS Full-text

DOCUMENT NUMBER: 98:71917

TITLE: Benzothiophene compounds

INVENTOR(S): Jones, Charles David

PATENT ASSIGNEE(S): Eli Lilly and Co., USA SOURCE: Eur. Pat. Appl., 107 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PAT	CENT 1	NO.			KINI	)	DATE			APE	PLICA	CION	NO.		DATE
						-									
EP	6250	3			A1		1982	1013		ΕP	1982	-301	737		19820401
	R:	BE,	CH,	DE,	FR,	GB,	IT,	LÚ,	NL,	SE	E				
AU	8282	265			Α		1982	1007		AU	1982	-822	55		19820401
AU	5556	58			B2		1986	1002							
GB	2097	788			Α		1982	1110		GB	1982	968	)		19820401
GB	2097	788			В		1985	0424							
JP	5718	1081			·A		1982	1108		JΡ	1982	-564	79		19820402
PRIORITY	APP	LN.	INFO	. :						US	1981	-246	335	Α	19810403
										US	1981	-3310	045	A	19811216

HO S OCH<sub>2</sub>CH<sub>2</sub>N Z

HO OCH<sub>2</sub>CH<sub>2</sub>N 
$$I$$

MeSO<sub>3</sub> OCH<sub>2</sub>CH<sub>2</sub>R

 $OCH_2$ CH<sub>2</sub>R

 $OCH_2$ CH<sub>2</sub>R

 $OCH_2$ CH<sub>2</sub>R

[(Aminoethoxy)benzoyl]benzothiophenes I (Z = CH2CH2CH2, CHMeCH2) were AB prepared, and limited the increase of uterine weight in rats treated with estradiol. Thus, treating II (R = Br) with 3-methylpyrrolidine in DMF containing KI gave II (R = 3-methyl-1-pyrrolidinyl) which was deprotected by NaOH to give I (Z = CHMeCH2).

L3 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1983:71916 CAPLUS Full-text

DOCUMENT NUMBER:

98:71916

TITLE:

3-(4-Aminoethoxybenzoyl)benzo[b]thiophenes

Jones, Charles David; Goettel, Mary Elizabeth

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA Eur. Pat. Appl., 59 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

INVENTOR(S):

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PA'	TENT NO.		KINI	DATE	APPLICATION NO.	DATE
	62504 62504		A1 B1	19821013 19860102	EP 1982-301738	19820401
	R: AT,	BE,	CH, DE,	FR, GB, IT,	LU, NL, SE	
US	4358593		A	19821109	US 1981-246334	19810403
IL	65378		Α	19860228	IL 1982-65378	19820330
CA	1167037		A1	19840508	CA 1982-400300	19820331
GB	2097392		Α	19821103	GB 1982-9679	19820401
GB	2097392		В	19850424		
DD	201793		A5	19830810	DD 1982-238654	19820401
CS	227348		B2	19840416	CS 1982-2357	19820401
PL	130867		B1	19840929	PL 1982-235752	19820401
AT	17243		T	19860115	AT 1982-301738	19820401
DK	8201512		A	19821004	DK 1982-1512	19820402
FI	8201160		Α	19821004	FI 1982-1160	19820402
JP	57183788		Α	19821112	JP 1982-56480	19820402
ES	511124		A1	19830616	ES 1982-511124	19820402
HU	28787		A2	19831228	HU 1982-1026	19820402
HU	191353		В.	19870227		
SU	1155157		A3	19850507	SU 1982-3417550	19820402

PRIORITY APPLN. INFO.:

US 1981-246334 A 19810403 US 1981-246335 A 19810403 US 1981-331045 A 19811216 EP 1982-301738 A 19820401

OTHER SOURCE(S):

MARPAT 98:71916

Benzothiophenes I [R = H; R1 = COC6H4O(CH2)2NR2R3-4; R2 = R3 = alkyl; R2R3 = (CH2)4-6, (CH2)2O(CH2)2, etc.] were prepared by Friedel-Crafts acylation of I (R = Ac, Bz, MeSO2; R1 = H) followed by hydrolysis of the ester groups. Thus, HSC6H4OMe-3 was treated with BrCH2COC6H4OMe-4 to give 3-MeOC6H4SCH2COC6H4OMe-4, which was cyclized with polyphosphoric acid to give I (R = Me, R1 = H). Demethylation of the latter followed by esterification with MeSO2Cl gave I (R = MeSO2, R1 = H; II). Friedel-Crafts acylation of 4 g II with 4-Me2N(CH2)2OC6H4COCl gave 6.2 g I [R = MeSO2, R1 = COC6H4O(CH2)2NMe2-4, III]. Hydrolysis of III gave I (R = H). I are estrogens, antiestrogens, and antiandrogens (no data).

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# http://www.cas.org/support/stngen/stndoc/properties.html

```
=> s e4
             1 "RALOXIFENE HYDROCHLORIDE"/CN
L4
=> d 14 1 ide
     ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
L4
RN
     82640-04-8 REGISTRY
     Entered STN: 16 Nov 1984
ED
     Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-
CN
     piperidinyl)ethoxy]phenyl]-, hydrochloride (1:1) (CA INDEX NAME)
OTHER CA INDEX NAMES:
     Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-
CN
     piperidinyl)ethoxy]phenyl]-, hydrochloride (9CI)
OTHER NAMES:
CN '
     Bonebay
     Bontact
CN
CN
     Evista
CN
     Fiona
CN
     Keoxifene hydrochloride
CN
     LY 156758
CN
     Ralofen
CN
     Raloxifene hydrochloride
CN
     Reloxafine
MF
     C28 H27 N O4 S . Cl H
CI
     COM
LC
                  ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
       BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, EMBASE, HSDB*,
       IMSPATENTS, IMSRESEARCH, IPA, MRCK*, MSDS-OHS, PATDPASPC, PHAR, PROMT,
```

PROUSDDR, PS, RTECS\*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL (\*File contains numerically searchable property data) CRN (84449-90-1)

HC1

### \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

329 REFERENCES IN FILE CA (1907 TO DATE) 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA 329 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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## http://www.cas.org/infopolicy.html

=> s 14

L5 329 L4

=> d scan

L5 329 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN

CC 63-6 (Pharmaceuticals)

TI Preparation of raloxifene hydrochloride capsules and establishment of its quality control standard

ST raloxifene hydrochloride capsules dissoln quality control

IT Drug delivery systems

(capsules; preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

IT Dissolution

Quality control

(preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

IT 63-42-3, Lactose 9004-32-4, Carboxymethyl cellulose sodium 9004-34-6, Cellulose, biological studies

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

IT 82640-04-8, Raloxifene hydrochloride

RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)

(preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

## HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

- L5 329 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN
- CC 2-4 (Mammalian Hormones)

Section cross-reference(s): 1

- TI Effectiveness of combined GnRH analogue plus raloxifene administration in the treatment of uterine leiomyomas: a prospective, randomized, single-blind, placebo-controlled clinical trial
- ST leuprolide acetate SERM raloxifene pelvic pain menorrhagia uterine leiomyomas
- IT Human

(GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Intestine, disease

(constipation; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Menopause

(hot flash; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Uterus, neoplasm

(leiomyoma; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Menstrual disorder

(menorrhagia; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Body, anatomical

(pelvis, pain; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Menopause

(premenopause; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Estrogen receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selective modulator of; GnRH analog (Enantone) plus raloxifene
hydrochloride (Evista) effectiveness in treatment of premenopausal
women with uterine leiomyomas)

IT Urinary system, disease

(urinary frequency; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT 74381-53-6, Leuprolide acetate

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (Enantone; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

82640-04-8, Raloxifene hydrochloride RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

#### HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1 CAPLUS COPYRIGHT 2007 ACS on STN 329 ANSWERS L5 IC ICM C07D333-64 ICS C07D333-56 27-9 (Heterocyclic Compounds (One Hetero Atom)) CC TΤ Demethylation process for preparing benzo[b]thiophenes demethylation benzothiophene benzenethiol ST 63675-73-0P 63675-74-1P 84541-36-6P ITRL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (demethylation process for preparing benzo[b]thiophenes) 63676-25-5P **82640-04-8P** 84449-87-6P ΙT 84449-90-1P 215662-11-6P 215662-12-7P RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation) (demethylation process for preparing benzo[b]thiophenes) 108-90-7, Chlorobenzene, uses TT RL: NUU (Other use, unclassified); USES (Uses) (demethylation process for preparing benzo[b]thiophenes) 7340-90-1 7446-70-0, Aluminum chloride, reactions IT 2632-13-5 15570-12-4, 3-Methoxybenzenethiol 84449-80-9 RL: RCT (Reactant); RACT (Reactant or reagent) (demethylation process for preparing benzo[b]thiophenes) HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1 CAPLUS COPYRIGHT 2007 ACS on STN L5 329 ANSWERS IC ICM A61K031-445 ICS A61K031-40; A61K031-38 INCL 514324000 63-6 (Pharmaceuticals) Section cross-reference(s): 1 TI Methods of decreasing serum calcium levels benzoyl benzothiophene calcium blood decrease; raloxifene calcium blood ŚТ decrease 82640-04-8, Raloxifene hydrochloride 84449-90-1, Raloxifene IT RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (benzoylbenzothiophene derivs. for decreasing serum calcium levels) 7440-70-2, Calcium, biological studies IT RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (benzoylbenzothiophene derivs. for decreasing serum calcium levels) HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1 CAPLUS COPYRIGHT 2007 ACS on STN L5 329 ANSWERS IÇ C12Q001-02 INCL 435029000 2-1 (Mammalian Hormones) CC Cell culture for screening estrogen agonists and antagonists TI estrogen agonist screening cell culture; antagonist estrogen screening ST

cell culture . Animal cell line

IT

```
(C7 MCF7-173, in screening of estrogen agonists/antagonists)
IT
     Estrogens
     RL: ANST (Analytical study)
        (agonists, cell culture method for screening of)
     Cell proliferation
IT
        (cells dependent on estrogens for, in screening of estrogen
        agonists/antagonists)
IT
     Charcoal
     RL: ANST (Analytical study)
        (dextran-, human serum stripped with, for maintaining medium in cell
        culture method for screening of estrogen agonists/antagonists)
TΤ
     Blood serum
        (fetal bovine, for maintaining medium in cell culture method for
        screening of estrogen agonists/antagonists)
     Animal tissue culture
IT
        (for estrogen agonist/antagonist screening)
IT
     Proteins, biological studies
     RL: BIOL (Biological study)
        (inhibitory to proliferation of estrogen-dependent cells in vitro, for
        cell culture method for screeing of estrogen agonists/antagonists)
IT
     Estrogens
     RL: PRP (Properties)
        (antiestrogens, cell culture method for screening of)
TΤ
     Mammary gland
        (neoplasm, cells of, in screening of estrogen agonists/antagonists)
IT
     50-27-1, Estriol 50-28-2, Estradiol, biological studies
     Estrone, biological studies
     RL: ANST (Analytical study)
        (agonists and antagonists of, cell culture method for screening of)
     9004-54-0, Dextran, biological studies
IT
     RL: BIOL (Biological study)
        (charcoal-, human serum stripped with, for maintaining medium in cell
        culture method for screening of estrogen agonists/antagonists)
     10540-29-1, Tamoxifen
                             34816-55-2, Moxestrol
                                                      63676-25-5, LY117018
     71794-60-0, 11\beta-Chloromethylestradiol 82640-04-8, LY156758
     120382-04-9, RU39411
                            57-83-0, Progesterone, biological studies
     RL: ANST (Analytical study)
        (estrogen agonist/antagonist activity of, determination of, cell culture
method
        for)
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0
=> s 14/prep
           329 L4
       4449106 PREP/RL
            34 L4/PREP
                 (L4 (L) PREP/RL)
=> d 16 ibib abs 1-
YOU HAVE REQUESTED DATA FROM 34 ANSWERS - CONTINUE? Y/(N):y
     ANSWER 1 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN
L6
                         2007:265820 CAPLUS Full-text
ACCESSION NUMBER:
DOCUMENT NUMBER:
                         146:448285
TITLE:
                         Benzothiophenes, formulations containing same, and
                         methods
                         Cullinan, George J.; Palkowitz, Alan D.
INVENTOR(S):
PATENT ASSIGNEE(S):
                         USA
```

Hung. Pat. Appl., 40pp.

SOURCE:

CODEN: HUXXCV

DOCUMENT TYPE:

Patent Hungarian

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
HU 9901882	A2	20000228	HU 1999-1882	19970219
HU 9901882	A3	20000328	,	
PRIORITY APPLN. INFO.:			HU 1999-1882	19970219
OTHER SOURCE(S):	MARPAT	146:448285		

Ι

GI

$$\begin{array}{c|c}
 & \text{OCH}_2\text{CH}_2\text{N} - \text{R}^3 \\
 & \text{R}^4
\end{array}$$

Benzothiophene N-oxides I [R1 = H, OH, alkoxy, OCO2(alkyl or aryl), OCO(alkyl or aryl), etc.; R2 = R1, Cl or F; R3 and R4 = alkyl or combine to form polymethylene or morpholine; X = CH2, CHOH, O or CO], useful for the treatment or prevention of medical indications associated with post-menopausal syndrome and breast cancer, are prepared Thus, [2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was oxidized using 30% aqueous H2O2 to give I [R1 = R2 = OH, R3R4 = (CH2)5, X = CO]. I reduce serum cholesterol compared to ovariectomized rats and do not cause a large increase in the number of eosinophils observed in the stromal layer of the ovariectomized rat uteri. In an osteoporosis test, I prevent bone loss in a general, dose-dependent manner. I were active in the MCF-7 proliferation assay and inhibited growth of DMBA-induced mammary tumors. A tablet formulation comprises: I 2.5-1000, cellulose 200-650, silicon dioxide 10-650, and stearic acid 5-15 mg/tablet.

L6 ANSWER 2 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2006:958171 CAPLUS Full-text

DOCUMENT NUMBER:

147:9760

TITLE:

Synthesis of raloxifene hydrochloride

AUTHOR(S):

Song, Yan-ling; Zhao, Yan-fang; Meng, Yan-qiu; Gong,

CORPORATE SOURCE:

Ping

Shenyang Institute of Chemical Technology, Faculty of Pharmaceutical-Engineering, Shenyang, 110142, Peop.

Rep. China

SOURCE:

Zhongguo Xinyao Zazhi (2005), 14(7), 882-884

CODEN: ZXZHA6; ISSN: 1003-3734

PUBLISHER:

Zhongguo Xinyao Zazhi Youxian Gongsi

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

AB The synthesis of raloxifene hydrochloride [i.e., [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methan one hydrochloride] is reported. The target compound was synthesized from 3-methoxybenzenethiol and 4-methoxy-α-bromo acetophenone via five steps,

including substitution, cyclization, Friedel-Crafts reaction, di-Me reaction and salt formation. The structure of the target compound was confirmed by IR, 1H-NMR and MS. This synthetic route required mild conditions and provided an improved yield and was easily controlled.

ANSWER 3 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:1257978 CAPLUS Full-text

DOCUMENT NUMBER:

144:135192

TITLE:

Manufacture of raloxifene-hydrochloride-containing medicines for treating bone fracture delayed union or

nonunion.

INVENTOR(S):

Zhang, Jianhao; Huang, Haibo

PATENT ASSIGNEE(S):

Peop. Rep. China

SOURCE:

Faming Zhuanli Shenqing Gongkai Shuomingshu, 8 pp.

CODEN: CNXXEV

DOCUMENT TYPE:

Patent

LANGUAGE:

Chinese

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1615860	Α	20050518	CN 2003-10113253	20031111
PRIORITY APPLN. INFO.:			CN 2003-10113253	20031111

The title medicines are manufd. from (by wt.) raloxifene hydrochloride (35-AB 45%) as effective components, diluent (50-60%), disintegrant (2-4%), lubricant (0.5-1%), and adhesive (2-3%). The medicines can be produced into various drug forms such as tablets, capsules, suspensions, powders, granules, solns., etc., and have advantages of short course of treatment, high recovery rate, etc.

L6 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:547361 CAPLUS Full-text

DOCUMENT NUMBER:

143:59836

TITLE:

A process for preparing benzoic acid derivatives,

useful as intermediates for preparation of raloxifene

INVENTOR(S):

Luke, Wayne Douglas

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA U.S. Pat. Appl. Publ., 10 pp.

CODEN: USXXCO

DOCUMENT TYPE:

Patent

LANGUAGE:

SOURCE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005137396	<b>A1</b>	20050623	US 2003-745188	20031222
US 7012153	B2	20060314		
PRIORITY APPLN. INFO.:			US 2003-745188	20031222

CASREACT 143:59836; MARPAT 143:59836 OTHER SOURCE(S):

The invention relates to a prepn. of benzoic acid derivs. of formula RO2C-p-C6H4-O(CH2)2-3N(R1)R2 [wherein: R is alkyl; R1 and R2 are independently alkyl, or combined together with the nitrogen atom form piperidinyl, pyrrolidinyl, or morpholinyl, etc.], useful as intermediates for preparation of raloxifene. For instance, 4-[2-(piperidin-1- yl)ethoxy]benzoic acid hydrochloride was prepared via etherification of Me 4-hydroxybenzoate by  $1-(\beta-$  chloroethyl)piperidine hydrochloride and subsequet hydrolysis with a yield of 99.2%.

REFERENCE COUNT:

9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2005:29327 CAPLUS Full-text

DOCUMENT NUMBER:

142:134465

TITLE:

Process for preparing raloxifene hydrochloride

INVENTOR(S):

Ferrari, Massimo; Zinetti, Fabrizio; Belotti, Paolo

PATENT ASSIGNEE(S):

Erregierre S.p.A., Italy

SOURCE:

PCT Int. Appl., 19 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT	NO.			KIN										D	ATE	
					-		<b></b> .							-		
WO 200	50031	16		<b>A1</b>		2005	0113	Ţ	WO 2	004-1	EP51:	263		2	0040	628
W :	ΑE,	AG,	AL,	AM,	ΑT,	AU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	ΚP,	KR,	KZ,	LC,
	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	ΜŻ,	NA,	NI,
	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
	ТJ,	TM,	TN,	TR,	TT,	TZ,	UA,	ŪĠ,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW
. RV	: BW,	GH,	GM,	KE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZM,	ZW,	AM,
	ΑZ,	BY,	KG,	ΚZ,	MD,	RU,	ТJ,	TM,	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,
	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,
	SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,
	SN,	TD,	TG													
CA 254	9354			A1		2005	0113	(	CA 20	004-	2549:	354		2	0040	628
EP 164	1773			<b>A1</b>		2006	0405	1	EP 20	004-	7419	07		2	0040	628
R:	ΑT,	ΒE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	MC,	PT,
	ΙE,	SI,	FI,	RO,	CY,	TR,	BG,	CZ,	EE,	HU,	PL,	SK				•
US 200	71001	47		A1		2007	0503	τ	JS 20	005-	5627	52 .		2	0051	227
PRIORITY AF	PLN.	INFO	. :						IT 20	003-1	MI13:	33	7	A 2	0030	630
								1	WO 20	004-1	EP512	263	1	N 2	0040	628

#### OTHER SOURCE(S): CASREACT 142:134465

A process for prepg. raloxifene hydrochloride with a purity greater than 98% AB and low aluminum content comprises the following stages : (a) demethylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene in pyridine and hydrochloric acid to obtain 6-hydroxy-2-(4- hydroxyphenyl)benzo[b]thiophene in pyridine hydrochloride, (b) acetylation of 6-hydroxy-2-(4hydroxyphonyl)benzo[b]thiophene with an acetylating agent to obtain the corresponding 6-acetoxy-2-(4- acetoxyphenyl)benzo[b]thiophene (I), (c) acylation of 6-acetoxy-2-(4- acetoxyphonyl)benzo[b]thiophene with 4-(2piperidinoethoxy) benzoylchloride hydrochloride with aluminum trichloride in a halogenated solvent to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl] - benzo[b]thiophene, (d) hydrolysis of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene according to the following operating conditions: (d1) treatment of 6-acetoxy-2-(4-acetoxyphonyl)-3-[4- (2-piperidinoethoxy)benzoyl]benzo[b]thiophene with alkaline hydroxide in alc. solvent, (d2) acidification of the product obtained in the preceding stage (d1) with a strong acid, to obtain the corresponding raloxifene salt with the strong acid, characterized in that the strong acid used in stage (d2) is concentrated hydrochloric acid. Thus, thionyl chloride was added to a mixture of 4-(2-piperidinoethoxy) benzoic acid HCl salt and pyridine in refluxing methylene chloride; the mixture was stirred for 1 h and

the solvent was distilled off; the mixture was cooled to 20°C, and I was added. The resulting mixture was mixed with aluminum trichloride in methylene chloride at 15°C to 30°C; the mixture was stirred for 1 h and was worked up : the product was treated with sodium hydroxide in methanol; water, Et acetate, and HCl were added; the suspension was centrifuged to give crude raloxifene hydrochloride.

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 6 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2004:617920 CAPLUS Full-text

DOCUMENT NUMBER:

142:463529

TITLE:

AUTHOR (S):

Synthesis of raloxifene hydrochloride Gong, Ping; Zhao, Yanfang; Wang, Dun

CORPORATE SOURCE:

School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, Peop.

Rep. China

SOURCE:

Shenyang Yaoke Daxue Xuebao (2003), 20(2), 111-113

CODEN: SYDXFF; ISSN: 1006-2858

PUBLISHER:

Shenyang Yaoke Daxue Xuebao Bianjibu

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

OTHER SOURCE(S):

CASREACT 142:463529

Raloxifene hydrochloride, which is a selective estrogen receptor modulator, AB was synthesized from 3-methoxybenzenethiol and 2-bromo- 4'-methoxyacetophenone by etherification, cyclization in the presence of polyphosphoric acid, hydrolysis with HBr/HOAc to obtain 6-hydroxy- 2-(4-

hydroxyphenyl) benzothiophene, acylation with acetic anhydride, acylation with 4-[2-(1-piperidinyl)ethoxy]benzoyl chloride in the presence of AlCl3, saponification with 5M NaOH solution in methanol, and saltification with HCl. The overall yield was 10.0%, and its structure was confirmed by MS, 1H NMR, 13C NMR.

ANSWER 7 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2002:348716 CAPLUS Full-text

DOCUMENT NUMBER:

138:137104

TITLE:

Synthesis of Raloxifene hydrochloride as selective

estrogen receptor modulator

AUTHOR (S):

Chen, Yanzhong; Liu, Yingxiang

CORPORATE SOURCE:

Guangdong College of Pharmacy, Canton, 510224, Peop.

Rep. China

SOURCE:

Guangdong Yaoxueyuan Xuebao (2002), 18(1), 1-3, 20

CODEN: GYXUF8

PUBLISHER:

Guangdong Yaoxueyuan

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

OTHER SOURCE(S):

CASREACT 138:137104

Raloxifene was synthesized from  $\alpha$ -bromo-p-methoxyacetophenone and mmethoxybenzenethiol via condensation, cyclization, acylation, and demethylation with the overall yield 49.2%. The chemical structure of compound was confirmed by 1H NMR, MS, IR, and elementary anal. The reaction conditions were mild and starting materials were com. available.

ANSWER 8 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2001:247325 CAPLUS Full-text

DOCUMENT NUMBER:

134:266100

TITLE:

Synthesis of 4-[(2-piperidin-1-yl)ethoxy]benzoic acid

for manufacture of Raloxifene hydrochloride

INVENTOR (S):

Luke, Wayne Douglas

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

PCT Int. Appl., 32 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

KIND	DATE	APPLICATION NO.	DATE
A2	20010405	WO 2000-US21974	20000918
AL, AM, AT	, AU, AZ,	BA, BB, BG, BR, BY,	BZ, CA, CH, CN,
CZ, DE, DK	, DM, DZ,	EE, ES, FI, GB, GD,	GE, GH, GM, HR,
IL, IN, IS	, JP, KE,	KG, KP, KR, KZ, LC,	LK, LR, LS, LT,
MA, MD, MG	, MK, MN,	MW, MX, MZ, NO, NZ,	PL, PT, RO, RU,
SG, SI, SK	C, SL, TJ,	TM, TR, TT, TZ, UA,	UG, US, UZ, VN,
ZW, AM, AZ	, BY, KG,	KZ, MD, RU, TJ, TM	
KE, LS, MW	, MZ, SD,	SL, SZ, TZ, UG, ZW,	AT, BE, CH, CY,
ES, FI, FR	GB, GR,	IE, IT, LU, MC, NL,	PT, SE, BF, BJ,
CI, CM, GA	, GN, GW,	ML, MR, NE, SN, TD,	TG
A2	20020710	EP 2000-966691	20000918
CH, DE, DK	E, ES, FR,	GB, GR, IT, LI, LU,	NL, SE, MC, PT,
LT, LV, FI	, RO, MK,	CY, AL	
T	20030318	JP 2001-526522	20000918
:		US 1999-156205P	P 19990927
		WO 2000-US21974	W 20000918
	A2 AL, AM, AT CZ, DE, DK IL, IN, IS MA, MD, MG SG, SI, SK ZW, AM, AZ KE, LS, MW ES, FI, FR CI, CM, GA A2 CH, DE, DK LT, LV, FI	A2 20010405 AL, AM, AT, AU, AZ, CZ, DE, DK, DM, DZ, IL, IN, IS, JP, KE, MA, MD, MG, MK, MN, SG, SI, SK, SL, TJ, ZW, AM, AZ, BY, KG, KE, LS, MW, MZ, SD, ES, FI, FR, GB, GR, CI, CM, GA, GN, GW, A2 20020710 CH, DE, DK, ES, FR, LT, LV, FI, RO, MK, T 20030318	A2 20010405 WO 2000-US21974  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, A2 20020710 EP 2000-966691  CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, LT, LV, FI, RO, MK, CY, AL T 20030318 JP 2001-526522 :

CASREACT 134:266100; MARPAT 134:266100 OTHER SOURCE(S):

An improved process for the prepn. of 4[(2-piperidin-1-yl)ethoxy]benzoic acid derivs. comprises reacting haloalkyl amine X(CH2)nNR1R2 (X = halogen; R1, R2 = C1-4 alkyl, combined with nitrogen atom to form piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, 1-hexamethyleneimino group; n = 2, 3) with C1-6 alkyl p-hydroxybenzoate in the presence of a hydrated inorg. base in an appropriate solvent.

CAPLUS COPYRIGHT 2007 ACS on STN L6 ANSWER 9 OF 34

ACCESSION NUMBER:

1999:12339 CAPLUS Full-text

DOCUMENT NUMBER:

130:66385

TITLE:

Process for preparing benzoic acid derivatives as intermediates in the synthesis of benzothiophenes

INVENTOR (S):

Chelius, Erik Christopher

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

U.S., 7 pp. CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 5852193	Α	19981222	US 1998-69277		19980429
US 6075146	Α	20000613	US 1998-123889		19980728
PRIORITY APPLN. INFO.:			US 1997-45162P	P	19970430
		•	US 1998-69277	<b>A3</b>	19980429
OTHER SOURCE(S):	CASREA	ACT 130:66385	5; MARPAT 130:66385		

# \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The title compds. [I; R1, R2 = C1-4 alkyl; NR1R2 = piperidino, pyrrolidino, morpholino, etc.; n = 2-3; R6 = carboxy protecting group] were prepared byreacting a hydroxylamine HO(CH2)nNR1R2 with a compound selected from W2O and W-halo (wherein W = p-toluenesulfonyl, methylsulfonyl, trifluoromethylsulfonyl, etc.) followed by reaction of the resulting Y1(CH2)nNR1R2 (Y1 = p-toluenesulfonyloxy, methylsulfonyloxy, trifluoromethylsulfonyloxy, etc.) with a compound II. Compds. I can be then reacted with benzothiophenes III (R4, R5 = hydroxy protecting groups) to afford compds. IV (R4, R5 = , H, hydroxy protecting groups) (example of such reaction was given).

REFERENCE COUNT: THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS 29 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

1.6 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1998:721690 CAPLUS Full-text

DOCUMENT NUMBER:

130:3769

Processes for preparing benzothiophenes TITLE:

McGill, John McNeil, III; Misner, Jerry Wayne; Zhang, INVENTOR(S):

Tony Yantao

PATENT ASSIGNEE(S): Eli Lilly and Co., USA PCT Int. Appl., 26 pp. SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT:

	TENT																ATE	
	9849																9980	428
							BB,											
							IS,											
		•	•	•	•	-	MN,					-	•					
							TT,											
	RW:	•	•	•	•	-	SD,	-			-	•	•			CI.	CM.	GA,
		•	-	•	•	•	TD,	•	•		•	•	•	•	• • •	•	•	
CA	2287		•		•		-			CA	199	8-2	287	943		. 1	9980	428
AU	9872	613			Α		1998	1124		AU	199	8-7	2613	3		1	9980	428
	9809																	
	2000																	
	2001																	
	6090						2000											
EP	8755	10																
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, I'	Τ,	LI,	LU,	NL,	SE,	MC,	PT,
		ΙΕ,	SI,	LT,	LV,	FI,	RO	•			•							
MX	9909	883	•	•	Α	-	2000	0331		MX	199	9-9	883			1	9991	027
PRIORIT	Y APP	LN.	INFO	. :						US	199	7 – 4	517	7 P		P 1	9970	430
										WO	199	8 - U	IS85(	9		W 1	9980	428
OTHER SO	OURCE	(s):			CASI	REAC	T 13	0:376	59;	MAR	PAT	13	0:37	769				

<sup>\*</sup> STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AΒ The title compds. [I, Y = Cl, Br, I, SO2(C1-4 alkyl), etc.] were prepd. by reacting benzo[b]thiophene II [R51, R52 = hydroxy protecting groups] with benzoyl chloride III [R8 = acyl activating group] in the presence of a boron trihalide such as BCl3. Compds. I were reacted further with an amine HNR6R7 [R6, R7 = C1-4 alkyl; NR6R7 = piperidino, pyrrolidino, morpholino, etc.] to produce benzothiophenes IV and their salts.

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 11 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1998:721501 CAPLUS Full-text

DOCUMENT NUMBER:

130:3768

TITLE:

Demethylation process for preparing benzo[b]thiophenes

INVENTOR (S):

Hoard, David Warren; Luke, Wayne Douglas

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

Eur. Pat. Appl., 13 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATION NO.	DATE
EP 875511	A1 19981104	EP 1998-303345	19980429
R: AT, BE, CH,	DE, DK, ES, FR, GB,	GR, IT, LI, LU, NL,	SE, MC, PT,
IE, SI, LT,	LV, FI, RO		
CA 2236254	A1 19981030	CA 1998-2236254	19980427
JP 11005789	A 19990112	JP 1998-118628	19980428
US 5994547	A 19991130	US 1998-69500	19980429
PRIORITY APPLN. INFO.:	•	US 1997-45156P	P 19970430
OTHER SOURCE(S):	CASREACT 130:3768;	MARPAT 130:3768	
GT .			

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

AB. The prepn. of benzo[b] thiophenes I [R1, R2 = C1-4 alkyl; NR1R2 = piperidino, pyrrolidino, etc.] by the acylation of alkoxy protected starting materials followed by demethylation of II using essentially odorless thiol compound (2methyl-5-t-Bu-benzenethiol) are provided herewith. Demethylation may be

II

carried out in the same reaction vessel without isolation of the acylated, protected material.

REFERENCE COUNT:

10

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 12 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN L6

ACCESSION NUMBER:

1998:721498 CAPLUS Full-text

DOCUMENT NUMBER:

130:3767

TITLE:

Process for preparing benzoic acid derivative intermediates and benzothiophene pharmaceuticals

INVENTOR(S): PATENT ASSIGNEE(S): Chelius, Erik Christopher Eli Lilly and Company, USA

SOURCE:

Eur. Pat. Appl., 16 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATION NO.	DATE			
EP 875507	A1 19981104	EP 1998-303340	19980429			
R: AT, BE, CH,	DE, DK, ES, FR, G	B, GR, IT, LI, LU, NL,	SE, MC, PT,			
IE, SI, LT,	LV, FI, RO	•				
CA 2231013	A1 19981030	CA 1998-2231013	19980304			
JP 10316674	A 19981202	JP 1998-116564	19980427			
PRIORITY APPLN. INFO.:		US 1997-45162P	P 19970430			
OTHER SOURCE(S):	CASREACT 130:3767	; MARPAT 130:3767	•			
GI						

The novel intermediates Y1(CH2)nNR1R2 [R1, R2 = C1-4 alkyl; NR1R2 = AB piperidino, pyrrolidino, morpholino, etc.; n = 2-3; Y1 = p-toluenesulfonyloxy, methylsulfonyloxy, trifluoromethylsulfonyloxy, 2,2,2trifluoroethylsulfonyloxy, trifluoroacetoxy], useful as intermediates in synthesis of benzothiophenes I and their salts, were prepared by reaction a hydroxylamine HO(CH2)nNR1R2 with W2O and W(halo) [W = p-toluenesulfonyl, methylsulfonyl, trifluoromethylsulfonyl, etc.].

REFERENCE COUNT:

19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 13 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN 1998:719256 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER:

130:3764

TITLE:

A regioselective alkylation process for preparing

substituted benzo[b]thiophenes

INVENTOR(S):

McGill, John McNeil, III; Miller, Randal Scot

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

PCT Int. Appl., 22 pp. CODEN: PIXXD2

Patent

DOCUMENT TYPE: LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATION NO.	DATE				
WO 9848792		WO 1998-US8477	19980428				
W: AL, AM, AT,	AU, AZ, BA, BB,	BG, BR, BY, CA, CH,	CN, CU, CZ, DE,				
DK, EE, ES,	FI, GB, GE, GH,	GM, GW, HU, ID, IL,	IS, JP, KE, KG,				
KP, KR, KZ,	LC, LK, LR, LS,	LT, LU, LV, MD, MG,	MK, MN, MW, MX,				
NO, NZ, PL,	PT, RO, RU, SD,	SE, SG, SI, SK, SL,	TJ, TM, TR, TT,				
UA, UG, US,	UZ, VN, YU, ZW,	AM, AZ, BY, KG, KZ,	MD, RU, TJ, TM				
RW: GH, GM, KE,	LS, MW, SD, SZ,	UG, ZW, AT, BE, CH,	CY, DE, DK, ES,				
FI, FR, GB,	GR; IE, IT, LU,	MC, NL, PT, SE, BF,	BJ, CF, CG, CI,				
CM, GA, GN,	ML, MR, NE, SN,	TD, TG					
CA 2287918	A1 19981105	CA 1998-2287918	19980428				
AU 9871653	A 19981124	AU 1998-71653	19980428				
EP 979075	A1 20000216	EP 1998-918798	19980428				
R: AT, BE, CH,	DE, DK, ES, FR,	GB, GR, IT, LI, NL,	SE, PT, IE, FI				
JP 2001523252	T 20011120	JP 1998-547259	19980428				
US 6025495	A 20000215	US 1998-69276	19980429				
PRIORITY APPLN. INFO.:		US 1997-45132P	P 19970430				
		WO 1998-US8477	W 19980428				
OTHER SOURCE(S):	CASREACT 130:37	64; MARPAT 130:3764					

$$\begin{array}{c} & & & \\ & &$$

The title benzo[b]thiophenes I [R1, R2 = C1-4 alkyl; NR1R2 = piperidino, AΒ pyrrolidino, morpholino, etc.; n = 2, 3] such as raloxifene, were prepared by the regioselective alkylation of benzothiophene II with Y(CH2)nNR1R2 [Y = Cl, p-TsO] in the presence of a suitable base.

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS 6

L6 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:192131 CAPLUS Full-text

DOCUMENT NUMBER: 128:275070

TITLE: Benzothiophenes, formulations containing same, and

methods

INVENTOR(S): Cullinan, George Joseph; Palkowitz, Alan David

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: U.S., 10 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	'			
US 5731342	A	19980324	US 1997-787041	19970127
PRIORITY APPLN. INFO.:			US 1997-787041	19970127
OTHER SOURCE(S):	MARPAT	128:275070		
GI				

$$X \longrightarrow OCH_2CH_2NR^3R^4$$
 $R^2$ 

Benzothiophene N-oxides [I; R1 = H, OH, alkoxy, OCO2(alkyl or aryl), OCO(alkyl or aryl), etc.; R2 = R1, Cl or F; R3 and R4 = alkyl or combine to form polymethylene or morpholine; X = CH2, CHOH, O or CO], useful for the treatment or prevention of medical indications associated with post-menopausal syndrome and breast cancer, are prepared Thus, [2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was oxidized using 30% aqueous H2O2 to give I [R1 = R2 = OH, R3R4 = (CH2)5, X = CO]. I reduce serum cholesterol compared to ovariectomized rats and do not cause a large increase in the number of eosinophils observed in the stromal layer of the ovariectomized rat uteri. In an osteoporosis test, I prevent bone loss in a general, dose-dependent manner. I were active in the MCF-7 proliferation assay and inhibited growth of DMBA-induced mammary tumors. A tablet formulation comprises: I 2.5-1000, cellulose 200-650, silicon dioxide 10-650, and stearic acid 5-15 mg/tablet.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:161136 CAPLUS Full-text

DOCUMENT NUMBER: 128:221639

TITLE: Preparation of amorphous benzothiophenes for

pharmaceuticals

INVENTOR(S): Cuff, George W.; Thakkar, Arvind L.

PATENT ASSIGNEE(S): Eli Lilly and Company, USA; Cuff, George W.; Thakkar,

Arvind L.

SOURCE: PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	PATENT NO.										DATE								
														768.		19970822			
		W:	AL,	AM,	AU,	AZ,	BA,	BB,	BG,	BR, B	Y,	CA,	CN,	CU,	CZ,	EE,	GE,	GH,	
			HU,	IL,	İS,	JP,	KE,	KG,	ΚP,	KR, K	Z,	LC,	LK,	LR,	LT,	LV,	MD,	MG,	
			MK,	MN,	MW,	MX,	NO,	NZ,	PL,	RO, R	U,	SD,	SG,	SI,	SK,	SL,	ТJ,	TM,	
			TR,	TT,	UA,	ŪĠ,	US,	UZ,	VN,	YU, Z	W						•		
		RW:	GH,	ΚE,	LS,	MW,	SD,	SZ,	UG,	ZW, B	F,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	
						SN,													
	ΕP	8266	82 -			A1 19980304					, 1	997-3	3064	26		1	9970	322	
	EP	8266	82			B1		2003	0312										
		R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB, G	R,	IT,	LI,	LU,	NL,	SE,	MC,	PT,	
			ΙE,	SI,	LT,	LV,	FI,	RO											
	CA	2263	175			A1		1998	0305	CA	1	997-2	2263	175		1	9970	322	
•	AU	9742	335			A B2		1998	0319	AU	1	997-4	4233	5		1	9970	322	
	AU	7239	87			B2		2000	0907										
,	IN	1829	40			<b>A</b> 1		1999	0814	IN	1	997-0	CA15	49		1	9970	322	
•						Α					_	997-		_					
	CN	1244	124			A A2		2000	0209	CN	1	997-	1974	34		1:	9970	322	
	HU	2000	0117	2		A2		2001	0628	HÜ	2	000-3	1172			1	9970	322	
	HU	2000	0117	2		A3		2002	0128										
	NZ	3338	39			Α		2001	0629	NZ	1	997-3	3338	39		1:	9970	322	
	$_{ ext{IL}}$	1286	41	•		Α		2001	1031	IL	1	997-	1286	41		1	9970	322	
	TR	9900	403			<b>T2</b>		2002	0121	TR	1	999-4	403			1:	9970	322	
	JΡ	2002	5141	74		T		2002	0514	JP	1	998-5	51174	44		1	9970	322	
	ΑT	2342	95			T			0315	AT	1	997-3	30642	26		1	9970	322	
	ES	2195	089			Т3				ES									
•	ZA	9707	617			A		1999				997-7					9970		
		6713								US 1997-918741							9970	325	
						Α						999-9					9990:	225	
					. A			2000	0626	26 KR 1999-701682									
PRIO	RIORITY APPLN. INFO.:								996-2										
											1	997-T	JS14'	768	V	<b>V</b> 1:	9970	322	
			101			142 TO TO	* **	100	~~~~										

OTHER SOURCE(S): MARPAT 128:221639

AB A method for prepg. an amorphous form of a benzothiophene such as raloxifene is described. Thus, raloxifene-HCl was prepared by a series of reactions starting from 3-methoxybenzenethiol and 4'-methoxyphenacyl bromide. A formulation contained PEG-1450 70, spray-dried lactose 1.5, colloidal SiO2 1.5, Polysorbate-80 2.0, and raloxifene-HCl 25%. The bioavailability of raloxifene-HCl and the pharmacol. effects of this compound on osteoporosis and hyperlipidemia were determined

REFERENCE COUNT:

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1997:640660 CAPLUS Full-text

1

DOCUMENT NUMBER: 127:307297

TITLE: Preparation of 3-[4-(2-aminoethoxy)benzoyl]-2-aryl-6-

hydroxybenzo[b]thiophenes.

INVENTOR(S): Jones, Charles David; McGill, John McNeill, III

PATENT ASSIGNEE(S): Eli Lilly and Co., USA; Jones, Charles David; McGill,

John McNeill, III

SOURCE: PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.		APPLICATION NO.	DATE
		WO 1996-US3934	19960320
W: AL, AM, AT,	AU, BB, BG, BR,	BY, CA, CH, CN, CZ, D	DE, DK, EE, ES,
FI, GB, GE,	HU, IS, JP, KE,	KG, KP, KR, KZ, LK, L	LR, LS, LT, LU,
LV, MD, MG,	MK, MN, MW, MX,	NO, NZ, PL, PT, RO, R	RU, SD, SE, SG,
SI, SK, TJ,	TM, TR, TT, UA,	UG, US, UZ, VN, AM, A	AZ, BY, KG, KZ,
MD, RU, TJ,	TM		•
RW: KE, LS, MW,	SD, SŻ, UG, AT,	BE, CH, DE, DK, ES, F	I, FR, GB, GR,
IE, IT, LU,	MC, NL, PT, SE,	BF, BJ, CF, CG, CI, C	CM, GA, GN, ML,
MR, NE, SN,	TD, TG		•
CA 2249406	A1 19970925	CA 1996-2249406	19960320
AU 9652586	A 19971010	AU 1996-52586	19960320
		EP 1996-908892	
R: AT, BE, CH,	DE, DK, ES, FR,	GB, GR, IT, LI, LU, N	IL, SE, PT, IE, FI
JP 2000506885	T 20000606	JP 1997-533424	19960320
US 6008377	A 19991228	US 1998-125848	19980821
PRIORITY APPLN. INFO.:	,	US 1996-13674P	
•		WO 1996-US3934	W 19960320
OTHER SOURCE(S):	CASREACT 127:30	7297; MARPAT 127:30729	7

Title compds. (I; R1 = H, OH; R2, R3 = alkyl; R2R3N = pyrrolidino, piperidino, hexamethyleneimino, morpholino; HX = HCl, HBr) were prepared by reaction of PhOCH2CH2NR2R3.HX (variables as above) with acyl derivative (II; R4 = H, alkoxy; R5 = alkyl; R6 = Cl, Br, OH) in the presence of BX3. Thus, 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene-3-carbonyl chloride (preparation given), and Ph 2-N-piperidinylethyl ether hydrochloride (preparation given) in 1,2-dichloroethane at 0° were treated with BCl3 in 1,2-dichloroethane at 0° followed by warming to 35° for 16-20 h to give 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride 1,2-dichloroethane solvate.

ANSWER 17 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN L6

1997:124441 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER: 126:143973

Diaryl vinyl sulfoxides, a process for their TITLE:

synthesis, and their use in the preparation of

benzothiophene derivatives

INVENTOR (S): PATENT ASSIGNEE(S): Aikins, James A.; Miller, Randal S.; Zhang, Tony Y. Eli Lilly and Co., USA; Aikins, James A.; Miller,

Randal S.; Zhang, Tony Y.

SOURCE:

PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	PATENT NO.			KIN	D	DATE		APPLICATION NO.							DATE			
WO									WC				63			19960	604	
	W:	AL,	AM,	AT,	AU,	AZ,	BB,	BG,	BR, E	ΒY,	CA,	CH,	CN,	CZ,	DE	, DK,	EE,	
		ES,	FI,	GB,	GE,	HU,	IL,	ıs,	JP, F	Œ,	KG,	KP,	KR,	KZ,	LK	, LR,	LS,	
									MW, N									
		SE,	SG	•														
	RW:	KE,	LS,	MW,	SD,	SZ,	UG,	AT,	BE, C	ЭН,	DE,	DK,	ES,	FI,	FR	, GB,	GR,	
		IE,	IT,	LU,	MC,	NL,	PT,	SE,	BF, E	IJ,	CF,	CG,	CI,	CM				
US	5659	087			Α		1997	0819	US	1	995-	4787	06			19950	607	
US	6372	945			В1		2002	0416	US	1	995-	4831	30			19950	607	
CA	2220	145			<b>A</b> 1		1996	1219	C.F	1	996-	2220	145			19960	604	
AU	9660	920			Α		1996	1230	ΑU	1	996-	6092	0			19960	604	
	6973																	
	8303								E	1	996-	9182	11			19960	604	
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB, G	R,	IT,	LI,	LU,	NL,	SE	, PT,	· IE,	
		SI,	LT,	LV,	FI													
	1192						1998	0909	CN	1 1	996-	1961	67			19960	604	
BR	9608	579.			Α		1999				996-					19960	604	
JP	1150	7061			T		1999	0622	JI	1	996-	5015	52			19960	604	
HU	9900	922			.A2		1999	0728	JI HU	J 1	999-	922				19960	604	
HU	9900	922					2000	0628										
NZ	3370	30			A A		2000	1124	NZ	1	996-3	3370	30			19960	604	
NZ	3370	31			A		2001	0126	N Z	: 1	996-3	3370	31			19960	604	
SG	1065	58			<b>A</b> 1		2.004	1029	SG	; 1	998-4	4999				19960	604	
NO	9705	578			A A A A		1997		NC	1	997-!	5578				19971 20001	203	
NO	5987								NC	2	000-	5987	·			20001	127	
CN	1341	596			Α		2002	0327	CN	1 2	000-	1307	79			20001	215	
PRIORITY	APP	LN.	INFO	. :					US	3 1	995-4	4787	06		Α	19950	607	
									US	1	995-4	4831	30		Α	19950	607	
																19960		
															W .	19960	604	
OTHER SO	URCE	(S):			CASI	REAC	T 12	6:143	3973;	MA	RPAT	126	:143	973				

GI

$$R^{1}$$
 $R^{2}$ 
 $R^{2$ 

The invention is directed to new diarylvinyl sulfoxides I [R1, R2 = H, alkoxy, AB arylalkoxy, halo, amino; R3 = thermally labile or acid-labile alkyl, alkenyl, or arylalkyl group], and to a new process for their synthesis. I are useful precursors for 2-aryl-substituted benzothiophenes II, which are in turn intermediates for the drugs III.HX [R1, R2 = H, halo, amino, OH; R4, R5 = alkyl; or NR4R5 = pyrrolidino, piperidino, hexamethyleneimino, morpholino; X = Cl, Br]. For instance, treatment of 4-MeOC6H4CH2COC6H4OMe-4 with TiCl4 in THF and reaction with Me3CSH and Et3N gave the vinyl sulfide (E)-4-MeOC6H4CH:C(SCMe3)C6H4OMe-4 [(E)-IV]. Alternatively, lithiation of 4-MeOC6H4CH2SCMe3 with BuLi and condensation with 4-MeOC6H4CHO gave (Z)-IV. Oxidation of either isomer of IV with a dilute AcOH solution of peracetic acid, in PhMe at -20°, gave the corresponding sulfoxide I [R1 = R2 = OMe; R3 = CMe3]. Dehydrative cyclization of, e.g., the (E)-sulfoxide, using p-MeC6H4SO3H catalyst under Dean-Stark conditions in PhMe, gave the benzothiophene II [R1 = R2 = OMe]. This was acylated by 4-(2piperidinoethoxy) benzoyl chloride HCl in the presence of BCl3 with concomitant demethylation to give the objective compound III.HCl [R1 = R2 = OH, NR4R5 = piperidino].

ANSWER 18 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER:

1997:113406 CAPLUS Full-text

DOCUMENT NUMBER:

126:117861

TITLE:

Process for the synthesis of benzo(b)thiophenes

Aikins, James A.; Zhang, Tony Y.

INVENTOR(S): PATENT ASSIGNEE(S):

Eli Lilly and Co., USA; Aikins, James A.; Zhang, Tony

Υ.

SOURCE:

PCT Int. Appl., 35 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

KIND APPLICATION NO. PATENT NO. DATE WO 9640676 A1 19961219 WO 1996-US9167 19960604 AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS,

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LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
             SE, SG
         RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
             IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA
                                19970225
                                             US 1995-484536
     US 5606076
                          Α
                                                                    19950607
     CA 2223096
                          Α1
                                19961219
                                             CA 1996-2223096
                                                                    19960604
     AU 9660921
                                19961230
                                             AU 1996-60921
                                                                    19960604
     AU 702928
                          B2
                                19990311
     EP 859770
                                19980826
                                             EP 1996-918212
                          Α1
                                                                    19960604
     EP 859770
                          В1
                                 19991208
             AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
             SI, LT, LV, FI
     CN 1192211
                                19980902
                                             CN 1996-195943
                                                                    19960604
     CN 1086699
                          В
                                20020626
     BR 9609062
                          Α
                                19990126
                                             BR 1996-9062
                                                                    19960604
     JP 11506789
                          Т
                                19990615
                                             JP 1997-501555
                                                                    19960604
     HU 9900912
                          A2
                                19990728
                                             HU 1999-912
                                                                    19960604 a
     HU 9900912
                          A3
                                20000328
                          В
                                20010730
     HU 219735
                          Т
                                19991215
                                             AT 1996-918212
     AT 187450
                                                                    19960604
                          T3
                                             ES 1996-918212
     ES 2140859
                                20000301
                                                                    19960604
                                             PT 1996-918212
     PT 859770
                          T
                                20000531
                                                                    19960604
     IL 131440
                          Α
                                20001031
                                             IL 1996-131440
                                                                    19960604
     IL 122378
                          Δ
                                20010319
                                             IL 1996-122378
                                                                    19960604
     NO 9705582
                          Α
                                             NO 1997-5582
                                19971203
                                                                    19971203
     GR 3032666
                          Т3
                                20000630
                                             GR 2000-400364
                                                                    20000214
PRIORITY APPLN. INFO.:
                                             US 1995-484536
                                                                 A 19950607
                                             IL 1996-122378
                                                                 A3 19960604
                                             WO 1996-US9167
                                                                 W 19960604
OTHER SOURCE(S):
                         CASREACT 126:117861; MARPAT 126:117861
     The present invention is directed to a process for the synthesis of 2-
     arylbenzo[b]thiophenes. E.g., 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene
     was prepared from desoxyanisoin and 2-methyl-2-propanethiol via tert-Bu 4,4'-
     dimethoxystilbenyl sulfoxide.
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CAPLUS COPYRIGHT 2007 ACS on STN L6 ANSWER 19 OF 34

ACCESSION NUMBER:

1996:649600 CAPLUS Full-text

DOCUMENT NUMBER:

125:266032

TITLE:

Phosphorous-containing benzothiophenes, their

preparation, their use in treating postmenopausal syndrome-associated indications and estrogen-dependent

Bryant, Henry U.; Dodge, Jeffrey A.; Nissen, Jeffrey

diseases, and pharmaceuticals containing them

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA Eur. Pat. Appl., 19 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

INVENTOR(S):

Patent

LANGUAGE:

SOURCE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE			
EP 729964	A1	19960904	EP 1996-300878	19960209			
EP 729964	B1	20010509					
·R: AT, BE, CH,	DE, DK	, ES, FR, G	BB, GR, IE, IT, LI, LU,	NL, PT, SE			
US 6479517	B1	20021112	US 1995-395944	19950228			
ES 2158242	Т3	20010901	ES 1996-300878	19960209			

CA 2169414	A1	19960829	CA	1996-2169414		19960213
JP 08259560	Α	19961008	JP	1996-25281		19960213
US 5998443	Α	19991207	US	1997-946842		19971008
PRIORITY APPLN. INFO.:			US	1995-395944	Α	19950228
OTHER SOURCE(S) .	маррат	125.266032				

GT

Phosphorus-contq. benzothiophene compds. I [R1, R2 = H, OH, halo, OPO(O-AB alkyl)2, OPO(0-aryl)2, OPO(alkyl)2, OPO(aryl)2, OPO3-2, in which not more than one of R1 and R2 may be H, OH or halo; R3, R4 = CO(CH2)3, CO(CH2)4, alkyl, or R3 and R4 combine to form, with the nitrogen to which they are attached, piperidine, morpholine, pyrrolidine, 3-methylpyrrolidine, 3,3dimethylpyrrolidine, 3,4-dimethylpyrrolidine, azepine, or pipecoline], and pharmaceutically acceptable salts thereof, are provided which are useful for the treatment of the various medical indications associated with postmenopausal syndrome, as well as estrogen-dependent diseases, including cancer of the breast, uterus and cervix. Also provided are intermediate compds. and processes useful for preparing the pharmaceutically active compds. of the invention, as well as pharmaceutical compns. containing compds. of the invention.

ANSWER 20 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN 1996:319150 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER:

125:86484

TITLE:

Preparation of vinyl sulfenic acid derivatives as

benzo[b] thiophene intermediates

INVENTOR(S):

Hoard, David W.; Luke, Wayne D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 15 pp. CODEN: USXXAM

DOCUMENT TYPE:

LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5512701	Α	19960430	US 1995-482692	19950607
CA 2224225	A1	19961219	CA 1996-2224225	19960604
WO 9640693	A1	19961219	WO 1996-US9460	19960604
W: AL, AM, AT,	AU, AZ,	BB, BG, B	R, BY, CA, CH, CN,	CZ, DE, DK, EE,
ES, FI, GB,	GE, HU,	IL, IS, J	P, KE, KG, KP, KR,	KZ, LK, LR, LS,
V.T. III T.V	MD MG	MK MN M	W MX NO NZ PL	PT. RO. RU. SD.

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SE, SG
         RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
             IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM
                                                                   19960604
     AU 9661003
                          Α
                                19961230
                                            AU 1996-61003
     AU 698076
                          B2
                                19981022
     EP 830362
                          A1
                                19980325
                                            EP 1996-918314
                                                                   19960604
            AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
             SI, LT, LV, FI
                                19980902
                                            CN 1996-195947
                                                                   19960604
     CN 1192215
                          Α
     CN 1068883
                          В
                                20010725
                                19990608
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     BR 9608847
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                                            JP 1997-501774
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                          A2
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                                                                   19971204
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                              19980128
     NO 9705633
                                                                   20001212
                                            CN 2000-130796
     CN 1330071
                          Α
                                20020109
                                            US 1995-482692
                                                                A 19950607
PRIORITY APPLN. INFO.:
                                            US 1995-483607
                                                                A 19950607
                                                                W 19960604
                                            WO 1996-US9460
OTHER SOURCE(S):
                         CASREACT 125:86484; MARPAT 125:86484
```

4-R1C6H4CH:C(R9)C6H4R2-4 [I; R1,R2 = H, (ar)alkoxy, halo, NH2; R9 = SR4; R4 = OSi(R)3, NR5R6, SR8; R = (ar)alkyl, aryl; R5, R6 = H, (ar)alkyl; NR5R6 =pyrrolidino, piperidino, etc.; R8 = (ar)alkyl, aryl] were prepared by treating I [R9 = SOR3; R3 = labile alk(en)yl or aryl] with a silylating agent optionally followed by reaction with HNR5R6 or HSR8. Thus, (E)-I (R1 = R2 = OMe)(II; R9 = SOCMe3)(preparation given) was treated with (Me2CSiNH)2CO in PhMe followed by Me2NH, in the same pot, to give I (R1 = R2 = OMe, R9 = SNMe2) as a mixture of (E) - and (Z) -isomers. The latter mixt was treated with TsOH to give 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophe ne.

ANSWER 21 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN 1996:307324 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER:

124:343103

TITLE:

Preparation of unsolvated crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy) benzoyl] benzo[b] thiophene

hydrochloride.

INVENTOR(S):

Smith Labell, Elizabeth; Luke, Wayne Douglas; McNeill

McGill, John, III; Miller, Randal Scot

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA Ger. Offen., 18 pp.

SOURCE:

CODEN: GWXXBX

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE			
DE 19534744	A1	19960321	DE 1995-19534744	19950919			
US 5629425	A	19970513	US 1994-308325	19940919			
IN 1995CA00614	Α	20050304	IN 1995-CA614	19950530			
IN 1995CA00615	Α .	20050304	IN 1995-CA615	19950530			
TW 389760	В	20000511	TW 1995-84105614	19950605			
TW 412534	В	20001121	TW 1995-84105613	19950605			
US 5731327	A	19980324	US 1995-467485	19950606			
EG 21479	Α	20011128	EG 1995-455	19950606			
US 6399778	B1	20020604	US 1995-469093	19950606			

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	S 6472531	B1	20021029		1995-469961	19950606
	\$ 2109882	A1	19980116	ES	1995-1774	19950913
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	L 1001196	A1	19960319	ИГ	1995-1001196	19950914
	L 1001196	C2	19970404 19970314	77	1995-7752	19950914
	A 9507752 A 9507753	A A	19970314		1995-7753	19950914
	L 115315	A	19990922		1995-115315	19950914
	L 115314	A	20000229		1995-115314	19950914
	L 125283 .	A	20010614		1995-125283	19950914
	N 1995CA01111	A	20051021		1995-CA1111	19950914
· ·	A 2158399	A1	19960320		1995-2158399	19950915
	A 2158399	C	20010320	CA		
	A 2158400	A1	19960320	CA	1995-2158400	19950915
	A 2158400	C	20061024	<b>-</b> 11		
	K 9501027	A	19960320	DК	1995-1027	19950915
	K 175903	B1	20050606	-10		
	K 9501028	A	19960320	DK	1995-1028	19950915
	K 175897	B1	20050530			
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RO	0 115259	B1	19991230	RO	1995-1619	19950915
· Ro	0 115260	B1	19991230	RO	1995-1620	19950915
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C	Z 292007	В6	20030716	CZ	1995-2402	19950915
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F.	I 112226	B1	20031114			•
	I 9504403	A	19960320		1995-4403	19950918
	R 2724655	A1	19960322	FR	1995-10921	19950918
	R 2724655	B1	19971114			
	3 2293382	A	19960327	GB	1995-19028	19950918
	3 2293382	В	19980819			
	3 2293602	A	19960403	GB	1995-19032	19950918
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	J 9531730	A	19960404	ΑŬ	1995-31730	19950918
	J 691955	B2	19980528		1005 21521	10050010
	J 9531731	A	19960404	ΑÜ	1995-31731	19950918
	J 692907	B2	19980618		1005 220217	10050010
	P 08176147	A	19960709	שני	1995-238211	19950918
	P 2860071	B2	19990224	CINT	1005_110620	19950919
	N 1127253	A	19960724 20011121	CIN	1995-118629	19950918
	N 1075069	B		מד,	1995-238209	19950918
	P 08193081	A B	19960730 19960820		1995-238209	19950918
	J 11177 J 11178	в В	19960820		1995-284	19950918
	R 9504059	A	19960820		1995-4059	19950918
	R 9504059	A	19960924		1995-4060	19950918
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CN 1068324
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                                                                    19950919
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             MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
             TJ, TM
         RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT,
             LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,
             SN, TD, TG
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                                                                    19970109
     DK 175886
                          В1
                                20050523
     CZ 290344
                          В6
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                                            US 2002-83179
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PRIORITY APPLN. INFO.:
                                            US 1994-308325
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                                             US 1995-427914
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                                             US 1995-469093
                                                                 A1 19950606
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                                                                 A3 19950914
                                             CZ 1995-2402
                                                                 A3 19950915
                                            DE 1995-19534744
                                                                 A1 19950919
                                            WO 1995-US11872
                                                                 W 19950919
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AB Title compd. (I) (raloxifene hydrochloride) having a specified X-ray diffraction pattern, was prepared Thus, 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (preparation given) and 4-(2-piperidinoethoxy)benzoyl chloride hydrochloride (preparation given) in CH2Cl2 was treated with BCl3 at 0 for 8 h and at 35° for 16 h to give I.1,2-dichloroethane of 86.8% purity. The latter in MeOH was treated with NaOH and activated C followed by filtration, treatment with HCl, and crystallization to give 99.1% pure I.

L6 ANSWER 22 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1996:256453 CAPLUS Full-text

DOCUMENT NUMBER: 124:289251

TITLE: Process for preparing benzoic acid derivative

intermediates and benzothiophene pharmaceutical agents

INVENTOR(S):

Kjell, Douglas Patton; Perry, Fred Mason

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA Eur. Pat. Appl., 18 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

SOURCE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.						DATE				PLICA									
						A1					EP 1995-306050									
									19980422											
		R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB	, GI	R, II	Ε,	IT,	LI,	LU,	ΝL	, PT	, SE	
	US S	JS 5631369				Α		1997	0520		US	1994	4-2	986	36			1994	0831	
	IL 128881					Α		2000	1206		IL	1999	5-1	288	81			1995	0828	
	CA 2	2157	236			A1		1,996	0301		CA	1999	5-2	157	236			1995	0830	
	FI S	9504	067			Α		1996	0301		FI	1999	5 - 4	067				1995	0830	
	HU 73141			A2		1996	0628		HU	199	5-2	537				1995	0830			
	HU 2	2221	21 .	•		B1		2003	0428											
	BR S	9503	846			Α		1996	0917		BR	1995	5 - 3	846				1995	0830	
	AT :	1653	55			T		1998	0515		ΑT	199	5 - 3	060	50			1995	0830	
	ES 2	2114	721			T3		1998	0601		ES	1999	5 - 3	060	50			1995	0830	
	TW 4	1279	75			В		2001	0401		TW	1995	5 - 8	410	9069			1995	0830	
	JP (	0811	9964			Α		1996	0514									1995	0831	
	US S	5750	688			Α		1998	0512							•		1996		
PRIO	PRIORITY APPLN. INFO.:		. :													1994				
	RIORIII AFFERT. INIO									ΙL	1995	5 - 1	150	92		Α3	1995	0828		
OTHER	0.01	man	101 .			MADD	7 177	104	20021											

OTHER SOURCE(S):

MARPAT 124:289251

GI

$$O(CH_2) \text{ nNR}^{1}R^2$$
 $O(CH_2) \text{ nNR}^{1}R^2$ 
 The present invention provides a novel process for prepg. novel compds. of formula HO2C(p-C6H4)O(CH2)nNR1R2 [R1, R2 = C1-C4 alkyl, combine to form piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; n = 2, 3] or a pharmaceutically acceptable salt thereof, comprising (a) reacting a haloalkyl amine of formula X(CH2)nNR1R2 [X = halo; R1, R2, and n are as defined above], with a compds. of formula RO2C(p-C6H4)OH [R = C1-C6 alkyl], in the presence of an alkyl acetate solvent and a base; (b) extracting the reaction product of step (a) with an aqueous acid; and (c) cleaving the ester of the reaction product from step (b) to form an acid. The present invention further provides a novel process for preparing compds. of Formula I [R1, R2 = C1-C4 alkyl, or combine to form piperidinyl, pyrrolidino, methylpyrrolidino, dimethylpyrrolidinyl, morpholino, dimethylamino, diethylamino, or 1-

hexamethyleneimino; R3, R4 = H, hydroxy protecting group; n = 2, 3] or a pharmaceutically acceptable salt thereof, comprising (a) reacting a haloalkyl amine of formula X(CH2) nNR1R2 [X = halo; R1, R2, and n are as defined above], with a compound of formula RO2C(p-C6H4)OH [R = C1-C6 alky], in the presence of an alkyl acetate solvent and a base; (b) extracting the reaction product from step (a) with an aqueous acid; (c) cleaving the ester of the reaction product from step (b) to form an acid; (d) reacting the extracted product from step (c) with a compound of formula II [R3 and R4 are as defined above], or a pharmaceutically acceptable salt thereof; (e) optionally removing R3 and R4 hydroxy protecting groups of the reaction product from step (d); and (f) optionally forming a salt of the reaction from either steps (d) or step (e).

L6 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:150242 CAPLUS Full-text

DOCUMENT NUMBER:

124:202950

TITLE:

Preparation of benzothiophene glucopyranosides as

antihyperlipidemics.

INVENTOR (S):

Dodge, Jeffrey Alan; Frolik, Charles Alan; Lindstrom,

ADDITION NO

Terry Donald; Lugar, Charles Willis Iii; Staten,

Gilbert Stanley

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 20 pp.

DAME

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

KIND

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

DAMENIO MA

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 683170	A1	19951122	EP 1995-303265	19950516
EP 683170	B1	19990922		
			B, GR, IE, IT, LI, LU,	NL, PT, SE
US 5567820	Α	19961022	US 1995-404701	19950315
US 6723739	B1	20040420	US 1995-405555	19950315
CA 2149501	A1	19951121	CA 1995-2149501	19950516
ZA 9503975	A	19961118	ZA 1995-3975	19950516
AT 184880	T	19991015	AT 1995-303265	19950516
ES 2136799	Т3	19991201	ES 1995-303265	19950516
AU 9520121	A	19951130	AU 1995-20121	19950517
AU 683734	B2	19971120		
JP 07316180	A	19951205	JP 1995-118338	19950517
FI 9502420	Α	19951121	FI 1995-2420	19950518
NO 9501954	Α	19951121	NO 1995-1954	19950518
NO 304686	B1	19990201		
CN 1116626	Α	19960214	CN 1995-106322	19950518
CN 1039013	В	19980708		
BR 9502079	Α	19960305	BR 1995-2079	19950518
HU 73788	A2	19960930	HU 1995-1466	19950518
HU 219335	В	20010328		
'IL 113780	Α	19990620	IL 1995-113780	19950518
GR 3032142	<b>T</b> 3	20000427	GR 1999-403228	19991215
US 2004167080	<b>A1</b>	20040826	US 2004-778865	20040212
PRIORITY APPLN. INFO.:			US 1994-246655	A 19940520
			US 1995-405555	A1 19950315

OTHER SOURCE(S):

CASREACT 124:202950

GI

AB Raloxifene metabolites (I) and (II) and their hydrochloride salts were prepared Thus, I and II, prepared from 6-tert-butyldimethylsilylraloxifene and 4'-tert-butyldimethylsilylraloxifene and Me 1,2,3,4-O-tetraacetyl-D-glucopyranuronate, at 1.3 mg/kg in rats decreased serum cholesterol by 44.5% and 56.8%, resp. Drug formulations are given.

L6 ANSWER 24 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:123714 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

124:155994

TITLE:

Pharmaceutical compositions containing

2-phenyl-3-aryoylbenzothiophenes for for inhibiting

I

bone loss and lowering serum cholesterol

INVENTOR(S):

Draper, Michael W.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Can. Pat. Appl., 31 pp.

CODEN: CPXXEB

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

: 1

PATENT NO	).	KIND	DATE	APPLICATION NO.	DATE
CA 214199	99	<b>A</b> 1	19950903	CA 1995-2141999	19950207
US 547884	<u> 1</u> 7	Α	19951226	US 1994-205012	19940302
ZA 95009	76	Α	19960807	ZA 1995-976	19950207
NZ 314699	•	Α	20000728	NZ 1995-314699	19950207
EP 674903	3	<b>A</b> 1	19951004	EP 1995-300842	19950210
R: 1	AT, BE, C	H, DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU	, NL, PT, SE
NO 95007	74	Α	19950904	NO 1995-774	19950228
RU 210002	24	C1	19971227	RU 1995-102778	19950228
RU 215027	75	C1	20000610	RU 1996-119781	19950228
AU 951355	51	Α	19950907	AU 1995-13551	19950301
AU 702575	5	B2	19990225		
JP 072678	361	Α	19951017	JP 1995-41769	19950301
JP 281838	34	B2	19981030		

BR 9500784	A	19951024	BR	1995-784		19950301
CN 1119530	A	19960403	CN	1995-100021		19950301
HU 72638	A2	19960528	HU	1995-634		19950301
JP 10291932	Α	19981104	JP	1998-107550		19950301
JP 10310525	A	19981124	JP	1998-107549		19950301
US 5610168	Α	19970311	US	1995-422289		19950414
US 5641790	Α	19970624	US	1995-422417		19950414
US 5747510	Α	19980505	US	1997-788984		19970127
US 39050	E1	20060328	US	2003-375274		20030227
PRIORITY APPLN. INFO.:			. US	1994-205012	Α	19940302
		•	JP	1995-41769	<b>A</b> 3	19950301
•	1		US	1995-422417	<b>A</b> 1	19950414

AB A method of inhibiting bone loss or resorption, or lowering serum cholesterol, comprises administering to a human in need thereof pharmaceutical compns. containing 2-phenyl-3-aryoylbenzothiophenes, salt or solvate thereof, in a low dosage amount Raloxifene (I) at 50-200 mg decreased LDL cholesterol in postmenopausal women and there was no changes in HDL cholesterol level. A capsule contained I 150, starch 150, starch flowable powder 397, and silicone fluid 350 3.0 mg.

L6 ANSWER 25 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1995:991025 CAPLUS Full-text

DOCUMENT NUMBER:

124:106673

TITLE:

Methods for lowering serum cholesterol

INVENTOR(S):

Black, Larry J.; Bryant, Henry U.; Cullinan, George

J.; Kauffman, Raymond F.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 14 pp. Cont.-in-part of U.S. Ser. No. 995, 222,

abandoned.
CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 2

PAT	ENT NO.	KIND	DATE	APPLICATION NO.	DATE
US	5464845	Α	19951107	US 1993-159159	19931130
TW	383306	В	20000301	TW 1993-82100751	19930204
RU	2123335	C1	19981220	RU 1993-55026	19931213
ZA	9309427	Α	19950615	ZA 1993-9427	19931215
SK	279271	B6	19980805	SK 1993-1421	19931215
IL	108042	Α	19980104	IL 1993-108042	19931216
CZ	283863	B6	19980617	CZ 1993-2790	19931216
HU	69686	A2	19950928	HU 1993-3676	19931220
HU	223342	B1	20040628		
RO	113806	B1	19981130	RO 1993-1739	19931220
$_{ m PL}$	177349	B1	19991029	PL 1993-301579	19931220
CA	2112017	A1	19940623	CA 1993-2112017	19931221
CA	2112017	С	20050614		
NO	9304740	Α	19940623	NO 1993-4740	19931221
AU	9352578	A	19940707	AU 1993-52578	19931221
ΑU	669235	B2	19960530		
BR	9305182	Α .	19940816	BR 1993-5182	19931221
JP	06234632	A	19940823	JP 1993-323825	19931222
JP	3197129	B2	20010813		
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CN	1043608	В	19990616		•
ΑT	233559	T	20030315	AT 1993-310438	19931222

ES 2193142
PRIORITY APPLN. INFO.:

T3 20031101

ES 1993-310438 US 1992-995222 19931222 B2 19921222

OTHER SOURCE(S):

MARPAT 124:106673

GI

$$\begin{array}{c|c} & \text{CO} & \text{OCH}_2\text{CH}_2\left(\text{CH}_2\right)_n\text{R}^2 \\ \\ \text{R}^1 & \text{I} \end{array}$$

AB A method of lowering serum cholesterol levels comprising administering to a patient a serum cholesterol lowering amount of a compound I wherein n is 0, 1 or 2; R is hydroxyl, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R1 is hydrogen, hydroxyl, chloro, bromo, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R2 is a heterocyclic ring (pyrrolidino, piperidino, or hexamethyleneimino); or a pharmaceutically acceptable salt or solvate thereof. The tested compds. lowered LDL without significantly affecting primary sex targets.

L6 ANSWER 26 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1995:934099 CAPLUS Full-text

DOCUMENT NUMBER:

123:339764

TITLE:

Processes for preparing 3-(benzoyl)-2-(4-

hydroxyphenyl) benzothiophenes

INVENTOR(S):

Dodge, Jeffrey Alan; Stocksdale, Mark Gregory

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

PATENT ASSIGNEE (S)

Eur. Pat. Appl., 19 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	`APPLICATION NO.	DATE
				,
EP 675121	A1	19951004	EP 1995-302076	19950328
R: AT, BE, CH,	DE, DK,	, ES, FR,	GB, GR, IE, IT, LI, LU,	NL, PT, SE
CA 2145614	A1	19951001	CA 1995-2145614	19950327
JP 07278138	A	19951024	JP 1995-73418	19950330
US 5808061	Α	19980915	US 1995-503444	19950717
PRIORITY APPLN. INFO.:			US 1994-220853	A 19940331
OTHER SOURCE(S):	CASREAG	CT 123:33	9764; MARPAT 123:339764	
GT				

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

The title compds. [I; R1R2 = C4-6 polymethylene, CH2CH(CH3)CH2CH2, AB CH2C(CH3)2CH2CH2, CH2CH2OCH2CH2] [e.g., [6-hydroxy-2-(4hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methan one hydrochloride], useful for the treatment of osteoporosis in post-menopausal women (no data), are prepared by: (a) coupling a benzothiophene (II; X = H) with a (hydroxyethyl)amine HOCH2CH2N(R1)R2 in the presence of P(Ph3) and di-Et azodicarboxylate; or (b) reacting a benzothiophene (II; X = CH2CH2Z; Z = leaving group) with pyrrolidine, piperidine, hexamethyleneimine, methylpyrrolidine, dimethylpyrrolidine, or morpholine; (c) deprotecting the 6and 4-position hydroxy groups of the reaction product of step (a) or step (b); and (d) optionally salifying or forming a solvate of the reaction product of step (c).

ANSWER 27 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER:

DOCUMENT NUMBER:

1995:661193 CAPLUS Full-text 123:111843

TITLE:

2-amino-3-aroylbenzo[b] thiophenes and methods for

preparing and using same to produce 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-hydroxyphenyl)]aminoethoxy) benzoyl] benzo[b] thiophene

INVENTOR (S):

Godfrey, Alexander G. Eli Lilly and Co., USA

PATENT ASSIGNEE(S): SOURCE:

U.S., 9 pp.

CODEN: USXXAM

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT NO.		KIND	DATE	APPLICATION NO.	DATE .
US 5420349		Α	19950530	US 1994-258641	19940610
CA 2192096		A1	19951221	CA 1995-2192096	19950607
WO 9534536		A1	19951221	WO 1995-US7399	19950607
W: AM,	AT, AU	J, BB, 1	BG, BR, BY,	CA, CH, CN, CZ, DE, DI	K, EE, ES, FI,
GB,	GE, H	J, IS,	JP, KE, KG,	KP, KR, KZ, LK, LR, L	r, LU, LV, MD,
MG,	MN, MV	7, MX, 1	NO, NZ, PL,	PT, RO, RU, SD, SE, SC	G, SI, SK, TJ,
TM,	TT				•
RW: KE,	MW, SI	), SZ, 1	UG, AT, BE,	CH, DE, DK, ES, FR, GI	B, GR, IE, IT,
LU,	MC, NI	, PT,	SE, BF, BJ,	CF, CG, CI, CM, GA, Gi	N, ML, MR, NE,
SN,	TD, TO	3			
AU 9528236		A	19960105	AU 1995-28236	19950607

EP	764150	A1	19970326	EP 1995-923804		19950607	
EP	764150	B1	19991027			•	
	R: AT, BE,	CH, DE,	DK, ES, FR,	GB, GR, IE, IT, LI,	LU, M	C, NL, PT, SE	
HU	76000	A2	19970630	HU 1996-3404		19950607	
HU	213834	В	19971028				
HU	76525	A2	19970929	HU 1996-3403		19950607	
HU	216272	В	19990528				
BR	9507968	Α	19971118	BR 1995-7968		19950607	
JP	10503175	T	19980324	JP 1996-502366		19950607	
AT	186050	T	19991115	AT 1995-923804		19950607	
ES	2139222	T3	20000201	. ES 1995-923804		19950607	
HU	217822	В	20000428	HU 1998-2648		19950607	
FI	9604854	Α	19961204	FI 1996-4854		19961204	
GR	3032409	Т3	20000531	GR 2000-400106		20000119	
PRIORITY	APPLN. INFO.	:		US 1994-258641	Α	19940610	
				. WO 1995-US7399	W	19950607	
OTHER SO	URCE(S):	CASI	REACT 123:11	1843; MARPAT 123:111	843		

OR''

GI

A group of 2-amino-3-aroyl-benzo[b]thiophenes (I) are prepd. by prepg. an  $\alpha$ -AB hydroxy thioacetamide 4-ROC6H4CH(OH)C(:S)NR9R9 (II) wherein R, R8 and R9 independently represent C1-C6 alkyl; comprising: (a) reacting an alkyl imidate of the formula 4-ROC6H4CH(OH)C(:NH.protic acid)OR''' where R''' is C1-C6 alkyl, with a sulfur compound to yield a thioester of the formula 4-ROC6H4CH(OH)C(:S)OR'''; (b) reacting the thioester with a dialkylamine of the formula HNR8R9 to yield the  $\alpha$ -hydroxy thioacetamide; said steps being conducted without isolation or purification of the thioester., cyclizing II, and subsequently acylating the benzo[b]thiophene to yield the 2-amino-3-aryl derivative These compds. may be treated with suitable Ph Grignard reagents, and after deprotection, yield 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thi ophene. %Thus, e.g., p-anisaldehyde was converted to p- methoxybenzaldehyde cyanohydrin (80% yield) and subsequently to the Me imidate 4-MeOC6H4CH(OH)C(:NH.HCl)OMe (85-90% yield); reaction of the latter with H2S/Me2NH afforded  $\alpha$ -(4-methoxy phenyl)- $\alpha$ -hydroxy- N,Ndimethylthioacetamide (70%) which was cyclized with methanesulfonic acid to 2-N, N-dimethylamino-6-methoxybenzo[b] thiophene (79%); acylation of the latter with 4-(2-piperidinoethoxy) benzoyl chloride hydrochloride (autocatalytic) afforded 2-N, N-dimethylamino-6-methoxy-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride (I; R = Me, R3 = R4 = Me, R'' = 2-piperidinoethyl; 74%) which underwent Grignard reaction with 4methoxyphenylmagnesium bromide to afford 2-(4-methoxyphenyl)-6- methoxy-3-[4-(piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride (90%); deprotection of the latter with AlCl3/propanethiol afforded 6-hydroxy-2-(4-hydroxyphenyl)-

3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thi ophene hydrochloride (95% yield).

ACCESSION NUMBER:

1995:362913 CAPLUS Full-text

DOCUMENT NUMBER:

122:213884

TITLE:

A chemical probe for the estrogen receptor: synthesis

of the 3H-isotopomer of raloxifene

AUTHOR (S):

Dodge, Jeffrey A.; Stocksdale, Mark G.; Jones, C.

David

CORPORATE SOURCE:

Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE:

Journal of Labelled Compounds & Radiopharmaceuticals

(1995), 36(1), 43-9

CODEN: JLCRD4; ISSN: 0362-4803

PUBLISHER:

Wiley Journal

DOCUMENT TYPE: LANGUAGE:

English

Radiolabeled raloxifene (LY156758) was prepd. by tritium gas hydrogenolysis of AR a 3-aroyl bis-brominated precursor. The requisite halogenated intermediate was accessed by regioselective aroylation of 6-methoxy-2-(4methoxyphenyl)benzo[b]thiophene with 3,5-dibromo-4-[2-(1piperdinyl)ethoxy|benzoyl chloride. Selective deprotection of the aryl Me ethers in the presence of the ethoxy side-chain followed by palladium catalyzed halogen-tritum exchange provided the target compound with a specific activity of 30.1 Ci/mmol.

ANSWER 29 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1987:433189 CAPLUS Full-text

DOCUMENT NUMBER:

107:33189

TITLE:

Treatment of mammary cancer

INVENTOR(S):

Black, Larry J.; Clemens, James A.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 10 pp. Cont. of U.S. Ser. No. 289,360,

abandoned. CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4656187	Α	19870407	US 1983-556875	19831201
IORITY APPLN. INFO.:			US 1981-289360 A	A1 19810803

PRI AB A method of inhibiting the growth of estrogen-dependent mammary cancers comprises administering about 20 mg/kg/day of a 1st compound 6-hydroxy-2-(4hydroxyphenyl)-3-[4-(2-pyrrolidinoethoxy)benzoyl]benzo[b]th iophene (I) and .apprx.5 mg/kg/day of a 2nd compound tamoxifen (II). Also, a pharmaceutical combination comprises .apprx.4 parts by weight of I and .apprx.1 part by weight of II. I hydrochloride was prepared by reacting 4-(2pyrrolidinoethoxy) benzoic acid with thionyl chloride and then with 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (prepared from 3-methoxybenzenethiol and  $\alpha$ -bromo-4-methoxyacetophenone). Oral doses of I 20 and II 5 mg/kg/day were given for 8 wks to rats with induced mammary tumors. Half of the rats receiving the combination treatment experienced a total regression of their tumors. The rest had only a very modest growth of their tumors during the treatment. A synergistic effect was shown.

ANSWER 30 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1984:448784 CAPLUS Full-text

DOCUMENT NUMBER:

101:48784

TITLE:

Antiestrogens. 2. Structure-activity studies in a series of 3-aroyl-2-arylbenzo[b]thiophene derivatives leading to [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride (LY 156758), a remarkably effective estrogen antagonist with only minimal intrinsic estrogenicity

AUTHOR(S):

Jones, Charles D.; Jevnikar, Mary G.; Pike, Andrew J.; Peters, Mary K.; Black, Larry J.; Thompson, Allen R.;

Falcone, Julie F.; Clemens, James A.

CORPORATE SOURCE:

Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE:

Journal of Medicinal Chemistry (1984), 27(8), 1057-66

CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE:

LANGUAGE:

Journal English

GI

AB In an effort to prep. nonsteroidal antiestrogens demonstrating greater antagonism and less intrinsic estrogenicity than those currently available, a series of 3-aroyl-2-arylbenzo[b]thiophene derivs. was synthesized. These compds. were prepared by Friedel-Crafts aroylation of appropriate O-protected 2-arylbenzo[b]thiophene nuclei with basic side-chain-bearing benzoyl chlorides followed by removal of the protective groups to provide the desired compds. containing both hydroxyl and basic side-chain functionality. A particularly useful method for the cleavage of aryl methoxy ethers without removal of (dialkylamino)ethoxy side chain functionality elsewhere in the mol. was AlCl3/EtSH. The benzothiophene derivs. were tested for their ability to inhibit the growth-stimulating action of estradiol on the immature rat uterus. Seemingly minor changes in the side-chain amine moiety had profound effects on the ability of the compds. to antagonize estradiol. Analogs having basic side chains containing cyclic (pyrrolidine, piperidine, and hexamethyleneamine) moieties had less intrinsic estrogenicity and antagonized estradiol action more completely than their noncyclic counterparts. The most effective antiestrogen in the series, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (I) [84449-90-1], elicited a modest uterotropic activity that did not increase with increasing dose. In antagonism of estradiol, I exhibited a degree of inhibition surpassing that of tamoxifen at any dose tested. The new benzothiophene antiestrogen also had high affinity for rat uterine cytoplasmic estrogen receptor and was an inhibitor of the growth of DMBA-induced rat mammary tumors.

L6 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1984:156501 CAPLUS Full-text

DOCUMENT NUMBER:

100:156501

TITLE:

Antiestrogenic and antiandrogenic benzothiophenes

INVENTOR(S):

Jones, Charles D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 23 pp. Cont.-in-part of U.S. Ser. No. 246,335,

abandoned.

CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US ^4418068	· A	19831129	US 1981-331042	19811216
ZA 8202247	Α	19831130	ZA 1982-2247	19820401
PRIORITY APPLN. INFO.:			US 1981-246335	A2 19810403
OTHER SOURCE(S):	CASRE	ACT 100:1565	01	
GT				

AB Antiandrogenic and antiestrogenic [(piperidinoethoxy)benzoyl]benzothiophen es I [R,R1 = H, R2CO; R2 = H, cycloalkyl, (un)substituted alkyl, Ph] were prepared Thus, 2-(4-hydroxyphenyl)benzo[b]thiophene-6-ol was esterified with MeSO2Cl and the diester subjected to Friedel-Crafts acylation with 4-(2-piperidinoethoxy)benzoyl chloride to give I (R = R1 = MeSO2). This was saponified to give I (R = R1 = H) (II). Immature female rats administered 0.03 µg estradiol propionate (III) s.c. together with 3 mg II s.c. daily for 4 d had average uterus weight of 21.3 mg. Those given III alone had average uterus weight of 65.9 mg. I also were effective as antiandrogens and as mammary tumor inhibitors.

Ι

L6 ANSWER 32 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1983:422309 CAPLUS Full-text

DOCUMENT NUMBER:

99:22309

TITLE:

Acylated benzothiophenes

INVENTOR(S):

Peters, Mary K.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 7 pp. Cont.-in-part of U.S. Ser. No. 246,333,

abandoned.

CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	<del>-</del> -			
US 4380635	Α	19830419	US 1981-331046	19811216
CA 1167036	A1	19840508	CA 1982-400262	19820331
EP 62505	A1	19821013	EP 1982-301739	19820401

EP	62505	•			B1		1985	0724				•		
•	R: 2	AT,	BE,	CH,	DE,	FR,	GB,	IT,	LU,	NI	L, SE			
GB	20966	8 0			Α		1982	1020	G	В	1982-9681			19820401
GB	20966	8 0			В		1985	0612			•			
DD	20179	4			<b>A</b> 5		1983	0810	I	D	1982-23865	3		19820401
CS	22734	7			B2		1984	0416	C	S	1982-2356			19820401
RO	84584				<b>A</b> 1		1984	0717	F	0	1982-10711	8		19820401
$\mathtt{PL}$	13058	4			B1		1984	0831	F	L	1982-23575	1		19820401
AT	14429				T		1985	0815	A	T	1982-30173	9		19820401
DK	82015	13			Α		1982	1004	Ε	K	1982-1513			19820402
FI	82011	61			Α		1982	1004	F	Ί	1982-1161			19820402
JP	57181	079			Α		1982	1108	J	ſΡ	1982-56481			19820402
ES	51112	3			. A1		1983	0216	E	S	1982-51112	3		19820402
HU	28746				<b>A2</b>		1983	1228	H	U	1982-1025			19820402
HU	19108	4			В		1987	0128						
SU	11380	28			A3		1985	0130	S	U	1982-34172	51		19820402
PRIORIT	Y APPLI	N. I	NFO.	. :					Ü	IS	1981-24633	3	A2	19810403
									υ	JS	1981-24633	5	Α	19810403
				•					Ü	IS	1981-33104	5	Α	19811216
									U	JS	1981-33104	6	A	19811216
									E	P	1982-30173	9	A	19820401

GI

The acylated benzothiophenones I (R,R1 = C1-4 alkyl, RR1 = polymethylene, AB CH2CHMeCH2CH2, CH2CH2OCH2CH2) were prepared by acylation-demethylation of benzothiophenes II. Thus, 3-MeOC6H4SN was treated with BrCH2COC6H4OMe-p followed by cyclization to give II, which was treated with AlCl3 and the acid chloride of 4-(2-piperidinoethoxy) benzoic acid to give I (NRR1 = piperidino).

L6 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER:

DOCUMENT NUMBER:

1983:71918 CAPLUS Full-text

98:71918

TITLE:

Acylated benzothiophenes

INVENTOR(S):

Peters, Mary Kathleen; Jones, Charles David

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 29 pp.

DOCUMENT TYPE:

CODEN: EPXXDW

LANGUAGE:

Patent

FAMILY ACC. NUM. COUNT:

English

PATENT NO.	KIND DATE	APPLICATION NO.	DATE
EP 62505 EP 62505	A1 19821013 B1 19850724	EP 1982-301739	19820401
R: AT, BE, CH,		LU, NL, SE	
US 4380635	A 19830419	US 1981-331046	19811216
AT 14429	T 19850815	AT 1982-301739	19820401
PRIORITY APPLN. INFO.:		US 1981-246333 A	19810403
		US 1981-246335 A	19810403
	•	US 1981-331045 A	19811216
		US 1981-331046 A	19811216
		EP 1982-301739 A	19820401
OTHER SOURCE(S):	MARPAT 98:71918	•	

AB 3-[4-(2-Aminoethoxy)benzoyl]benzothiophenes I [R, R1 = C1-4 alkyl; RR1 = (CH2)4, (CH2)5, (CH2)6, CH2CHMeCH2CH2, CH2CH2OCH2CH2], useful as antiestrogens (no data), were prepared by acylating benzothiophene II. Thus, heating 3-MeOC6H4SCH2COC6H4OMe-4 with polyphosphoric acid gave II, which was acylated by 4-(Me2NCH2CH2O)C6H4CO2H.HCl and SOCl2 in PhCl-CH2Cl2 containing DMF and AlCl3 to give I (R = R1 = Me).

Ι

L6 ANSWER 34 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1983:71917 CAPLUS Full-text

DOCUMENT NUMBER:

98:71917

TITLE:

Benzothiophene compounds

INVENTOR(S):

Jones, Charles David

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 107 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

Énglish

FAMILY ACC. NUM. COUNT:

PAT	CENT	NO.			KIN	D	DATE		i	APP	LICAT	CION 1	10.	. 1	DATE
EP	6250	3			A1	_	1982	1013	]	EP	1982	30173	 37		19820401
	R:	BE,	CH,	DE,	FR,	GB	, IT,	LU,	NL,	SE	:				
ΑU	8282	265			Α		1982	1007	1	ΑU	1982-	-82269	5		19820401

AU 555658		B2	19861002				
GB 2097788		Α	19821110	GB	1982-9680		19820401
GB 2097788		В	19850424				
JP 57181081	(	Α	19821108	JP	1982-56479		19820402
PRIORITY APPLN. INFO.	:			US	1981-246335	Α	19810403
·				US	1981-331045	Α	19811216

GI

AB [(Aminoethoxy)benzoyl]benzothiophenes I (Z = CH2CH2CH2, CHMeCH2) were prepared, and limited the increase of uterine weight in rats treated with estradiol. Thus, treating II (R = Br) with 3-methylpyrrolidine in DMF containing KI gave II (R = 3-methyl-1-pyrrolidinyl) which was deprotected by NaOH to give I (Z = CHMeCH2).

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- NEWS 8 MAY 22 CA/CAplus enhanced with IPC reclassification in Japanese patents
- NEWS 9 JUN 27 CA/CAplus enhanced with pre-1967 CAS Registry Numbers
- NEWS 10 JUN 29 STN Viewer now available
- NEWS 11 JUN 29 STN Express, Version 8.2, now available
- NEWS 12 JUL 02 LEMBASE coverage updated
- NEWS 13 JUL 02 LMEDLINE coverage updated
- NEWS 14 JUL 02 SCISEARCH enhanced with complete author names
- NEWS 15 JUL 02 CHEMCATS accession numbers revised
- NEWS 16 JUL 02 CA/CAplus enhanced with utility model patents from China
- NEWS 17 JUL 16 CAplus enhanced with French and German abstracts
- NEWS 18 JUL 18 CA/CAplus patent coverage enhanced
- NEWS 19 JUL 26 USPATFULL/USPAT2 enhanced with IPC reclassification
- NEWS 20 JUL 30 USGENE now available on STN
- NEWS 21 AUG 06 CAS REGISTRY enhanced with new experimental property tags
- NEWS 22 AUG 06 BEILSTEIN updated with new compounds
- NEWS 23 AUG 06 FSTA enhanced with new thesaurus edition
- NEWS 24 AUG 13 CA/Caplus enhanced with additional kind codes for granted patents
- NEWS 25 AUG 20 CA/CAplus enhanced with CAS indexing in pre-1907 records

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                   RALOX LC/CN
                   RALOX-A/CN
E2
             1
             1 --> RALOXIFENE/CN
E3
E4
                RALOXIFENE HYDROCHLORIDE/CN
E5
             1
                   RALOZAM/CN
E6
             3
                   RALSTONITE/CN
E7
                   RALSTONITE (ALF2 (OH))/CN
             1
E8
                   RALSTONITE (ALF2 (OH) .1/2H2O)/CN
             1
                 RALTAT 10/CN
E9
             1
                   RALTEGRAVIR POTASSIUM/CN
E10
             1
                   RALTITREXED/CN
E11
             1
                   RALUBEN/CN
E12
             1
=> s e3
             1 RALOXIFENE/CN
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     ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN
     84449-90-1 REGISTRY
ED
     Entered STN: 16 Nov 1984
     Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-
     piperidinyl)ethoxy[phenyl] - (CA INDEX NAME)
OTHER NAMES:
CN
     Keoxifene
CN
     LY 139481
CN
     Raloxifene
     [2-(4-Hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl][4-(2-(1-
CN
     piperidinyl) ethoxy) phenyl] methanone
MF
     C28 H27 N O4 S
CI
     COM
                  ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
LC
     STN Files:
       BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU,
       DRUGU, EMBASE, HSDB*, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA,
       MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, RTECS*, SCISEARCH,
       SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:
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## \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1751 REFERENCES IN FILE CA (1907 TO DATE)
38 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1763 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus
COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION

FULL ESTIMATED COST

8.25 8.46

FILE 'CAPLUS' ENTERED AT 13:29:27 ON 21 AUG 2007
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FILE COVERS 1907 - 21 Aug 2007 VOL 147 ISS 9 FILE LAST UPDATED: 20 Aug 2007 (20070820/ED)

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# http://www.cas.org/infopolicy.html

=> s l1

L2 1763 L1

=> d scan

L2 1763 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN

CC 1-0 (Pharmacology)

TI Osteoporosis treatment and limitations and perspectives

ST review bisphosphonate raloxifene parathyroid hormone fall prevention disuse syndrome

IT Bone, disease

(fracture; osteoporosis treatment and limitations and perspectives)

IT Anabolic agents

Osteoporosis

(osteoporosis treatment and limitations and perspectives)

IT Diphosphonates RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (osteoporosis treatment and limitations and perspectives) 13598-36-2D, Phosphonic acid, alkylidenebis-derivs. ITRL: BSU (Biological study, unclassified); BIOL (Biological study) (Bisphosphonate; osteoporosis treatment and limitations and perspectives) 9002-64-6, Parathyroid hormone IT RL: BSU (Biological study, unclassified); BIOL (Biological study) (osteoporosis treatment and limitations and perspectives) IT **84449-90-1**, Raloxifene 129318-43-0 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (osteoporosis treatment and limitations and perspectives) HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1 CAPLUS COPYRIGHT 2007 ACS on STN 1763 ANSWERS L2 1-1 (Pharmacology) CC Validation of a novel HPLC method for the determination of Raloxifene and TI its pharmacokinetics in rat plasma ST Raloxifene detn plasma HPLC; liq chromatog Raloxifene plasma; pharmacokinetics Raloxifene plasma Blood plasma ΙT Pharmacokinetics (pharmacokinetics of Raloxifene in blood plasma of rats after oral dose) IT Blood analysis HPLC (validation of novel HPLC method for determination of Raloxifene and its pharmacokinetics in rat plasma) **84449-90-1**, Raloxifene IT RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study) (validation of novel HPLC method for determination of Raloxifene and its pharmacokinetics in rat plasma) HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1 L2 1763 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN CC 1-8 (Pharmacology) Effect of genistein and raloxifene on vascular dependent platelet TI aggregation genistein raloxifene antiplatelet platelet aggregation blood vessel STIT Blood vessel Cardiovascular system, disease Platelet aggregation Platelet aggregation inhibitors (effect of genistein and raloxifene on vascular dependent platelet aggregation) IT Estrogen receptors RL: BSU (Biological study, unclassified); BIOL (Biological study) (effect of genistein and raloxifene on vascular dependent platelet aggregation) Phytoestrogens IΤ RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (effect of genistein and raloxifene on vascular dependent platelet

aggregation)

10102-43-9, Nitric oxide, biological studies IT 9001-84-7, Phospholipase A2 35121-78-9, Prostacyclin

RL: BSU (Biological study, unclassified); BIOL (Biological study) (effect of genistein and raloxifene on vascular dependent platelet aggregation)

IT 446-72-0, Genistein 84449-90-1, Raloxifene

> RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of genistein and raloxifene on vascular dependent platelet aggregation)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> s l1/prep

1763 L1

4449106 PREP/RL

L3

38 L1/PREP

(L1 (L) PREP/RL)

=> d 13 4 ibib abs

ANSWER 4 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN 2005:1180831 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER:

145:356564

TITLE:

The advance of synthetic studies on selective estrogen

receptor modulators

AUTHOR (S):

Hu, Xiao; Zhu, Yujin; Yuan, Pengfei; Wu, Dan

CORPORATE SOURCE:

Fourth Brigade of Pharmacy, Medical College of Chinese

People's Armed Police Force, Tianjin, 300162, Peop.

Rep. China

SOURCE:

Wujing Yixueyuan Xuebao (2005), 14(2), 151-156

CODEN: WYXUA9; ISSN: 1008-5041 Wujing Yixueyuan Xuebao Bianjibu

PUBLISHER:

DOCUMENT TYPE:

Journal; General Review

LANGUAGE:

Chinese

A review on progress of synthesis of two series selective estrogen receptor modulators (SERMs): (phenyl)stilbenes and benzoheterocycles. A review on the synthesis of tamoxifen, droloxifene, raloxifene, toremifene, idoxifene, levormeloxifene and their derivs.

=> d 13 ibib abs 1-

YOU HAVE REQUESTED DATA FROM 38 ANSWERS - CONTINUE? Y/(N):y

ANSWER 1 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER:

DOCUMENT NUMBER:

2007:70746 CAPLUS Full-text

TITLE:

147:172240 Control of pharmaceuticals and animal health products

in wastewater effluents from manufacturing sites

AUTHOR(S):

Parke, Neil J.; Good, Nanci F.; Meyerhoff, Roger D. Lilly Corporate Center, Eli Lilly and Co.,

CORPORATE SOURCE: Indianapolis, IN, 46285, USA

SOURCE:

WEFTEC.05, Conference Proceedings, Annual Technical Exhibition & Conference, 78th, Washington, DC, United States, Oct. 29-Nov. 2, 2005 (2005), 145-155. Water

Environment Federation: Alexandria, Va.

CODEN: 69JOAM

DOCUMENT TYPE:

Conference; (computer optical disk)

LANGUAGE: English

In many cases, the discharge of pharmaceuticals and animal health products at bulk manufacturing, fill/finish, development and research operations may not be directly regulated with numeric limitations as a part of a facility's wastewater discharge permit. The biol. activity of these discharged compds., if not properly managed, may have the potential to impact the operation of an onsite or a municipal wastewater treatment plant, aquatic species in streams, rivers, oceans, or a drinking water source. An overview of the Eli Lilly and Company environmental protection program is provided, which shows how potential releases of active ingredients from its operations are managed to protect the environment.

REFERENCE COUNT:

THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS 12 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 2 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3

ACCESSION NUMBER:

2006:1063108 CAPLUS Full-text

DOCUMENT NUMBER:

145:417029

TITLE:

Methods for generating stably linked complexes composed of homodimers, homotetramers or dimers of

dimers

INVENTOR(S):

Chien, Hsing Chang; Goldenberg, David M.; McBride,

William J.; Rossi, Edmund A.

PATENT ASSIGNEE(S):

IBC Pharmaceuticals, Inc., USA

SOURCE:

PCT Int. Appl., 105 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PAT	rent 1	NO.			KIN	D :	DATE			APPL	ICAT	ION 1	NO.		D	ATE	
WO	2006	 1076	 17		A2	-	 2006	1012	WO 2006-US10762						20060324		
	W:	ΑE,	AG,	AL,	AM,	AT,	AU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	ΒZ,	CA,	CH,
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		KZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,	MN,	MW,	MX,
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		GM,	ΚE,	LS,	MW,	ΜZ,	NA,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZM,	ZW,	AM,	ΑZ,	BY,
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US	2007	0869	42		A1		2007	0419	1	US 2	006-	4780	21		2	0060	629
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             KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:
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                                            US 2005-751196P
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                                                                   20060314
                                            US 2005-389358
                                                                A2 20060324
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                                            WO 2006-US10762
                                                                A 20060324
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                                                                A2 20060328
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                                            US 2005-478021
                                                                A2 20060629
                                            US 2006-478021
                                                                A 20060629
                                            WO 2006-US25499
                                                                A2 20060629
                                            US 2006-864530P
                                                                P 20061106
     The authors disclose dimerization and docking domain (DDD) sequences for the
AB
     generation of stably tethered structures of defined compns., which may have
     multiple functionalities and/or binding specificities. The tethered
     constructs may be virtually any mol. or structure, such as antibodies,
     antibody fragments, antibody analogs or mimetics, aptamers, binding peptides,
     fragments of binding proteins, known ligands for proteins or other mols.,
     enzymes, detectable labels or tags, therapeutic agents, toxins,
     pharmaceuticals, cytokines, interleukins, interferons, radioisotopes,
     proteins, peptides, peptide mimetics, polynucleotides, RNAi, oligosaccharides,
     natural or synthetic polymeric substances, nanoparticles, quantum dots,
     organic or inorg. compds., etc. In one example, a fusion construct of a DDD
     sequence with an anti-CEA Fd fragment was prepared and shown to target
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20070426

A2

WO 2007047609

WO 2006-US40431

AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,

20061016

L3 ANSWER 3 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:958171 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER: 147:9760

TITLE: Synthesis of raloxifene hydrochloride

AUTHOR(S): Song, Yan-ling; Zhao, Yan-fang; Meng, Yan-qiu; Gong,

colorectal cancer in a xenograft model.

Ping

CORPORATE SOURCE: Shenyang Institute of Chemical Technology, Faculty of

Pharmaceutical-Engineering, Shenyang, 110142, Peop.

Rep. China

SOURCE: Zhongguo Xinyao Zazhi (2005), 14(7), 882-884

CODEN: ZXZHA6; ISSN: 1003-3734

PUBLISHER:

Zhongquo Xinyao Zazhi Youxian Gongsi

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

AB The synthesis of raloxifene hydrochloride [i.e., [6-hydroxy-2-(4-

hydroxyphenyl) benzo [b] thien-3-yl] [4-[2-(1-piperidinyl) ethoxy] phenyl] methan one

hydrochloride] is reported. The target compound was synthesized from 3-methoxybenzenethiol and 4-methoxy- $\alpha$ -bromo acetophenone via five steps,

including substitution, cyclization, Friedel-Crafts reaction, di-Me reaction and salt formation. The structure of the target compound was confirmed by IR, 1H-NMR and MS. This synthetic route required mild conditions and provided an

improved yield and was easily controlled.

L3 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:1180831 CAPLUS Full-text

DOCUMENT NUMBER:

145:356564

TITLE:

The advance of synthetic studies on selective estrogen

receptor modulators

AUTHOR (S):

Hu, Xiao; Zhu, Yujin; Yuan, Pengfei; Wu, Dan

CORPORATE SOURCE:

Fourth Brigade of Pharmacy, Medical College of Chinese

People's Armed Police Force, Tianjin, 300162, Peop.

Rep. China

SOURCE:

Wujing Yixueyuan Xuebao (2005), 14(2), 151-156

CODEN: WYXUA9; ISSN: 1008-5041

PUBLISHER:

Wujing Yixueyuan Xuebao Bianjibu

DOCUMENT TYPE:

Journal; General Review

LANGUAGE:

Chinese

AB A review on progress of synthesis of two series selective estrogen receptor modulators (SERMs): (phenyl)stilbenes and benzoheterocycles. A review on the synthesis of tamoxifen, droloxifene, raloxifene, toremifene, idoxifene,

levormeloxifene and their derivs.

L3 ANSWER 5 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:708484 CAPLUS Full-text

DOCUMENT NUMBER:

143:221841

TITLE:

Estrogen receptor ligands. Dihydrobenzoxathiin SERAMs

with an optimized antagonist side chain

AUTHOR (S):

Blizzard, Timothy A.; DiNinno, Frank; Chen, Helen Y.; Kim, Seongkon; Wu, Jane Y.; Chan, Wanda; Birzin, Elizabeth T.; Yang, Yi Tien; Pai, Lee-Yuh; Hayes, Edward C.; DaSilva, Carolyn A.; Rohrer, Susan P.;

Schaeffer, James M.; Hammond, Milton L.

CORPORATE SOURCE:

Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE:

Bioorganic & Medicinal Chemistry Letters (2005),

15(17), 3912-3916

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER:

Elsevier B.V.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 143:221841

AB An optimized side chain for dihydrobenzoxathiin SERAMs was discovered and attached to four dihydrobenzoxathiin platforms. The novel SERAMs show

exceptional estrogen antagonist activity in uterine tissue and an MCF-7 breast cancer cell assay.

REFERENCE COUNT:

2.7

THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:451379 CAPLUS Full-text

DOCUMENT NUMBER:

142:487547

TITLE:

Antiresorptive mutual salt of raloxifene and

bisphosphonic acid

INVENTOR(S):

Ha, Tae Hee; Kim, Won Jeoung; Yun, Sangmin; Kim, Cheol Kyung; Kim, Han Kyong; Suh, Kwee-Hyun; Lee, Gwan Sun

PATENT ASSIGNEE(S): Hanmi Pharm. Co., Ltd., S. Korea

SOURCE:

PCT Int. Appl., 26 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DAT	<del></del>		
WO 2005047282 A1 20050526 WO 2004-KR2954 200	41115		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, C	A, CH,		
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, G	B, GD,		
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, L	C, LK,		
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, N	I, NO,		
NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, S	Y, TJ,		
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, Z	W, AM,		
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, D	E, DK,		
EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, P	T, RO,		
SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, M	L, MR,		
NE, SN, TD, TG			
KR 2005046883 A 20050519 KR 2003-80494 200	31114		
EP 1689744 A1 20060816 EP 2004-800095 200	41115		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, M	C, PT,		
IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS			
US 2007082871 A1 20070412 US 2006-579199 200	60512		
PRIORITY APPLN. INFO.: KR 2003-80494 A 200	A 20031114		
WO 2004-KR2954 W 200	41115		

OTHER SOURCE(S): MARPAT 142:487547

AB The mutual salt of raloxifene and bisphosphonic acid exhibits unexpectedly synergistic effects of two components to enhance bone mineral d. (BMD), control blood-calcium d., and lower the serum cholesterol level. For example, 3.2 g of alendronic acid was mixed with 5.0 g of raloxifene in 75 mL of ethanol/75 mL of water to obtain 6.5 g of raloxifene alendronate pentahydrate. A soft or hard capsule was prepared containing raloxifene alendronate pentahydrate 30 mg, lactose 215 mg, magnesium stearate 2 mg, and colloidal silica 3 mg. When given to female rats, the mutual salt of raloxifene and alendronic acid markedly enhanced BMD, bone stiffness, trabecular volume and bone volume, and also effectively controlled the blood cholesterol and calcium level through the synergic effects of its two components, as compared with the individual raloxifene hydrochloride or alendronate.

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:617920 CAPLUS <u>Full-text</u> DOCUMENT NUMBER: 142:463529

4

TITLE: · AUTHOR (S): Synthesis of raloxifene hydrochloride Gong, Ping; Zhao, Yanfang; Wang, Dun

CORPORATE SOURCE:

School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, Peop.

Rep. China

SOURCE:

Shenyang Yaoke Daxue Xuebao (2003), 20(2), 111-113

CODEN: SYDXFF; ISSN: 1006-2858

PUBLISHER:

Shenyang Yaoke Daxue Xuebao Bianjibu

DOCUMENT TYPE: LANGUAGE:

Journal Chinese

OTHER SOURCE(S):

CASREACT 142:463529

Raloxifene hydrochloride, which is a selective estrogen receptor modulator, was synthesized from 3-methoxybenzenethiol and 2-bromo- 4'-methoxyacetophenone by etherification, cyclization in the presence of polyphosphoric acid, hydrolysis with HBr/HOAc to obtain 6-hydroxy- 2-(4hydroxyphenyl)benzothiophene, acylation with acetic anhydride, acylation with 4-[2-(1-piperidinyl)ethoxy]benzoyl chloride in the presence of AlCl3, saponification with 5M NaOH solution in methanol, and saltification with HCl. The overall yield was 10.0%, and its structure was confirmed by MS, 1H NMR, 13C NMR.

L3

ANSWER 8 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2004:292022 CAPLUS Full-text

DOCUMENT NUMBER:

140:309411

TITLE:

Pharmaceutical compositions comprising raloxifene acid

addition salts and/or solvates

INVENTOR (S):

Karup, Gunnar Leo; Pedersen, Soren Bols

PATENT ASSIGNEE(S):

A/S Gea Farmaceutisk Fabrik, Den.

SOURCE:

PCT Int. Appl., 64 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PAT	PATENT NO.			KIN	KIND DATE				APPLICATION NO.						DATE			
	2004						2004			WO 2	003-1	DK64	5		20	0030	930	
WO.	2004	0290	46		<b>A</b> 3		2004	1014										
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EP	1546	138			A2		2005	0629		EP 2	003-	7478	47		20	0030	930	
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PRIORITY	APP	LN.	INFO	.:						DK 2	002-	1450		7	A 20	0020	930	
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OTHER SOURCE(S): MARPAT 140:309411

Raloxifene acid addn. salts or solvates thereof, having improved dissoln. properties in media comprising hydrochloric acid are described, compared with similar prepns. based on raloxifene or raloxifene-hydrochloride. disclosed acid addition salts or solvates thereof show an improved bioavailability in media comprising hydrochloric acid, such as the gastric The acid addition salts or solvates thereof are addition salts or solvates of raloxifene and a pharmaceutically acceptable acid selected among succinic acid, lactic acid, malonic acid or sulfuric acid. Further, crystalline forms of the raloxifene salts and solvates thereof are disclosed. The raloxifene acid addition salts and/or solvates thereof are useful for the preparation of pharmaceutical composition for oral administration capable of fast and reliable release of the active ingredients in the stomach of the patient, in particular for the treatment of cancer or osteoporosis, or for inhibiting cartilage degradation A new method for preparation of raloxifene lactate is also disclosed. Thus, raloxifene malonate was prepared by the reaction of raloxifene-HCl with malonic acid in propanol-water solution The product was characterized by IR spectra and x-ray diffraction.

L3 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:269853 CAPLUS Full-text

DOCUMENT NUMBER:

2004:269853 CAPLUS <u>Full-text</u> 140:309370

TITLE:

Amino acid and peptide carriers for oral delivery of

active agent

INVENTOR(S):

Piccariello, Thomas; Kirk, Randal J.; Olon, Lawrence

Р.

UG, US, UZ, VN, YU, ZA, ZW

PATENT ASSIGNEE(S):

SOURCE:

New River Pharmaceuticals Inc., USA
U.S. Pat. Appl. Publ., 176 pp., Cont.-in-part of U.S.

Pat. Appl. 2002 128,177.

CODEN: USXXCO

DOCUMENT TYPE:

LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT: 24

		APPLICATION NO.	DATE
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US 7060708	B2 20060613		
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The present invention relates to oral delivery systems of active agent, and more specifically to compns. that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for oral administration of conjugated active agent compns. For example, a polyserine-furosemide conjugate was prepared and its in vivo performance was examined Compared to parent furosemide, the conjugate showed a sustained drug release. The 9 h serum level of the polyserine-furosemide conjugate was 95.5% of its 3 h level, whereas the 9 h serum level of the parent drug was only 59.8% of its 3 h level.

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L3 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2003:726588 CAPLUS Full-text
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DOCUMENT NUMBER:

139:345292

TITLE:

Nitrosation, nitration, and autoxidation of the selective estrogen receptor modulator raloxifene by

nitric oxide, peroxynitrite, and reactive

nitrogen/oxygen species

AUTHOR (S):

Toader, Violeta; Xu, Xudong; Nicolescu, Adrian; Yu,

Linning; Bolton, Judy L.; Thatcher, Gregory R. J.

CORPORATE SOURCE: Department of Medicinal Chemistry and Pharmacognosy,

College of Pharmacy, University of Illinois at

Chicago, Chicago, IL, 60612-7231, USA

SOURCE: Chemic

Chemical Research in Toxicology (2003), 16(10),

1264-1276

CODEN: CRTOEC; ISSN: 0893-228X

PUBLISHER:

American Chemical Society

DOCUMENT TYPE: Journal LANGUAGE: English

The regulation of estrogenic and antiestrogenic effects by selective estrogen AB receptor modulators (SERMs) provides the basis for use in long-term therapy in cancer chemoprevention and postmenopausal osteoporosis. However, the evidence for carcinogenic properties within this class requires study of potential pathways of toxicity. There is strong evidence for the elevation of cellular levels of NO in tissue treated with SERMs, including the benzothiophene derivative, raloxifene, in part via up-regulation of nitric oxide synthases. Therefore, the reactions of  $17\beta$ -estradiol (E2), raloxifene, and an isomer with NO, peroxynitrite, and reactive nitrogen/oxygen species (RNOS) generated from NO2-/H2O2 systems were examined Peroxynitrite from bolus injection or slow release from higher concns. of 3-morpholinosydnonimine (SIN-1) reacted with the benzothiophenes and E2 to give aromatic ring nitration, whereas peroxynitrite, produced from the slow decomposition of lower concns. of SIN-1, was relatively unreactive toward E2 and yielded oxidation and nitrosation products with raloxifene and its isomer. The oxidation and nitrosation products formed were characterized as a dimer and quinone oxime derivative Interestingly, the reaction of the benzothiophenes with NO in aerobic solution efficiently generated the same oxidation products. Stable quinone oximes are not unprecedented but have not been previously reported as products of RNOSmediated metabolism The reaction of glutathione (GSH) with the quinone oxime gave both GSH adducts from Michael addition and reduction to the corresponding o-aminophenol. The ready autoxidn. of raloxifene, observed in the presence of NO, is the first such observation on the reactivity of SERMs and is potentially a general phenomenon of significance to SERM chemical toxicol.

REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2003:491620 CAPLUS Full-text

DOCUMENT NUMBER: 139:179942

TITLE: Synthesis of Constrained Raloxifene Analogues by

Complementary Use of Friedel-Crafts and Directed

Remote Metalation Reactions

AUTHOR(S): Kalinin, Alexey V.; Reed, Mark A.; Norman, Bryan H.;

Snieckus, Victor

CORPORATE SOURCE: Department of Chemistry, Queen's University, Kingston,

ON, K7L 3N6, Can.

SOURCE: Journal of Organic Chemistry (2003), 68(15), 5992-5999

CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:179942

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB New constrained heterocyclic analogs of Raloxifene, I [R1 = 2-(1-piperidinyl)ethoxy, R2 = H; R1 = H, R2 = 2-(1-piperidinyl)ethoxy] and II, were prepared by complementary Directed remote Metalation (DreM)/Friedel-Crafts cyclization approaches. Utilization of a benzylidene-thiolactone rearrangement was successfully implemented to construct benzothiophenes III (R3 = Me2CH, R4 = MeO; R3 = Me, PhCH2, R4 = Et2N) in good yields. Selective deprotection of III (R3 = Me2CH, R4 = MeO; R3 = PhCH2, R4 = Et2N) induced by complexation was followed by trifluoromethylsulfonylation and Suzuki-Miyaura

cross coupling with 3-[2-(1-piperidinyl)ethoxy]phenyl dioxaborolane to give the corresponding 2,4-diaryl-substituted benzothiophenes with methoxycarbonyl or diethylcarbamoyl group in the 3 position. Treatment of the latter with BCl3 or with excess LDA induced an intramol. para or ortho cyclization and concomitant double deprotection to furnish I. Similar sequence starting from III (R3 = Me, R4 = Et2N) afforded the constrained analog II.

REFERENCE COUNT:

THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2002:408662 CAPLUS Full-text

DOCUMENT NUMBER:

136:401637

TITLE:

Preparation of 3-arylbenzothiophenes by

cyclodehydration of phenylthioacetophenones using

activated clay or zeolite catalysts.

INVENTOR(S):

Luke, Wayne Douglas; Sanderson, Heidi Ann; Zheng, Hua

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

PCT Int. Appl., 26 pp.

DOCUMENT TYPE:

Patent

CODEN: PIXXD2

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

	PAT	CENT 1	NO.			KIN	D .	DATE			APPL	ICAT	ION I	NO.		D	ATE	
	WO.	2002	0422	 89		A2	-	2002	0530	1	 WO 2	001-	US42	940		2	 0011	 114
•		2002				A3		2002										
	WO	2002	0422	89		A8		2004	0212									
		W:	AE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	BZ,	CA,	CH,	CN,
								DK,										
			GM,	HR,	HU,	ID,	ΙL,	IN,	ıs,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	LK,	LR,
			LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PH,	PL,
			PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	TJ,	TM,	TR,	TT,	TZ,	UA,	UG,
			US,	UZ,	VN,	YU,	ZA,	ZW										
		RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZW,	AM,	AZ,	BY,	KG,
			KZ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	CH,	CY,	DE,	DK,	ES,	FI,	FR,	GB,	GR,
			IE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,
			GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	TG								
	ΑU	2002	0304	09		<b>A</b> 5		2002	0603		AU 2	002-	3040	9		2	0011	114
	US	2004	1327	75		A1		2004	0708	1	US 2	003-	4155	59		2	0030	922
	US	6921	827			B2		2005	0726									
PRIOR	(TIS	APP	LN.	INFO	. :					1	US 2	000-	2532	12P		P 2	0001	127
•										1	WO 2	001-1	JS42	940	•	W 2	0011	114
OTHER GI	S SC	URCE	(S):			CASI	REAC	T 13	6:40	1637	; MA	RPAT	136	:401	537			

Title compds. (I; R1, R2 = H, protecting group) were prepd. by cyclodehydration of phenylthioacetophenones (II; variables as above) in the presence of acid activated clays or acid activated zeolites and in the presence of solvents. Thus, PhMe, α-(3-methoxyphenylthio)-4-methoxyacetophenone, and "acid-activated clay" (Engelhard X-9107) were combined and refluxed 2 h using a Dean Stark trap. By HPLC the product mixture consisted of 96.7% 6-methoxy-3-(4-methoxyphenyl)benzo[b]thiophene, 1.1% 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene, 2.1% 4-methoxy-3-(4-methoxyphenyl)benzo[b]thiophene, and 0.1% 4-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene.

L3 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2002:408636 CAPLUS Full-text

DOCUMENT NUMBER:

136:401533

TITLE:

Coupling reaction process for preparing  $\alpha\text{-}(3\text{-arylthio})\,\text{acetophenones}$  from thiophenol derivs. and  $\alpha\text{-}(\text{leaving group})\,\text{-substituted}$ 

acetophenones

INVENTOR(S):

Luke, Wayne Douglas; Sanderson, Heidi Ann; Zheng, Hua

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

PCT Int. Appl., 17 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	PATENT NO.						DATE			APPL	ICAT:	ION I	NO.		D	ATE	
						-									-		
WO	2002	0422	61		A2		2002	0530	1	WO 2	001-	US42	939		2	0011	114
WO	2002	0422	61		<b>A3</b>		2003	0306	•								
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑT,	AU,	ΑZ,	BA,	BB,	BG,	.BR,	BY,	BZ,	CA,	CH,
		CN,	CO,	CR,	CU,	CZ,	CZ,	DE,	DE,	DK,	DK,	DM,	DZ,	EC,	EE,	EE,	ES,
		FI,	FI,	GB,	GD,	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KΕ,	KG,
		ΚP,	KR,	ΚZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,
		MX,	ΜZ,	NO,	NZ,	PH,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SK,	SL,
		ТJ,	TM,	TR,	TT,	TZ,	UA,	UG,	US,	UΖ,	VN,	YU,	ZA,	ZW,	AM,	ΑZ,	BY,
		KG,	KZ,	MD,	RU												
'	RW:	GH,	GM,	KΕ,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZW,	AT,	BE,	CH,	CY,
		DE,	DK,	ES,	FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,	BF,
	•	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	TG	
AU	2002	0285	93		A5		20.02	0603	7	AU 2	002-2	2859	3		2	0011	114
PRIORIT	Y APP	LN.	INFO	. :					1	US 2	000-2	2530	73P	]	2	0001	127
															√ 2	0011	114
OTHER S	THER SOURCE(S):					REAC	T 13	6:40	1533	; MAI	RPAT	136	:401	533			

 $R^{1}-0$  S  $O-R^{2}$ 

 $\alpha$ -(3-Arylthio)acetophenones [I; R1, R2 = H, hydroxy-protecting group; e.g.,  $\alpha$ -(3-methoxyphenylthio)-4-methoxyacetophenone] are prepared in high yield and

GI

selectivity by the coupling of a thiophenol derivative 3-(R10)C6H4SH (e.g., 3-methoxybenzenethiol) in an aqueous alkaline (e.g., KOH) solvent (e.g., Et acetate) with an aromatic ketone LCH2COC6H4(OR2)-4 (L = leaving group; e.g.,  $\alpha$ -chloro-4-methoxyacetophenone).

L3 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2001:283971 CAPLUS Full-text

DOCUMENT NUMBER:

134:300772 -

TITLE:

Glycosides and orthoester glycosides of raloxifene and

analogues and the use thereof

INVENTOR(S):

Holick, Michael Francis; Ramanathan, Halasya Strakan Group PLC, UK

PATENT ASSIGNEE(S):

PCT Int. Appl., 28 pp.

SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	PATENT NO.						DATE		1	APPL	ICAT	ION :	NO.		D.	ATE	
						_									-		
	WO 2001	0271	29		A1		2001	0419	1	WO 2	000-	GB38	64		2	0001	006
	W:	ΑE,	AG,	AL,	AM,	AT,	AU,	ΑZ,	BA,	BB,	BG;	BR,	BY,	BZ,	CA,	CH,	CN,
		CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,	HR,
		HU,	ID,	IL,	IN,	IS,	JP,	KΕ,	KG,	ΚP,	KR,	KZ,	LC,	LK,	LR,	LS,	LT,
		LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PL,	PT,	RO,	RU,
	SD, SE, SC				SI,	SK,	SL,	TJ,	TM,	TR,	TT,	TZ,	UA,	ŪĠ,	US,	UZ,	VN,
		YU,	ZA,	ZW,	AM,	ΑZ,	BY,	KG,	KZ,	MD,	RU,	TJ,	TM				
	RW:	GH,	GM,	ΚE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZW,	ΑT,	BE,	CH,	CY,
		DE,	DK,	ES,	FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	ΒF,	ВJ,
		CF,	CG,	CI,	CM,	GΑ,	GN,	GW,	ML,	MR,	ΝE,	SN,	TD,	TG			
	GB 2355007						2001	0411	(	GB 1	999-	2810	0		1	9991	126
PRIO	PRIORITY APPLN. INFO.:								1	US 1	999-	1581	41P	]	P 1	9991	800
									1	US 2	000-	2315	73P	]	P 2	0000	911

OTHER SOURCE(S): MARPAT 134:300772

Raloxifene and raloxifene analog glycosides and orthoester glycosides afford greater serum bioavailability of the hydroxylated parent compound, and are useful for treating or preventing a number of conditions that may be treated with an anti-estrogenic or an anti-androgenic compound. To a mixture of 0.5 g raloxifene and 1.6 g silver silicate in dry acetonitrile was added 3 g mol. sieves and stirred for 20 min. To the above suspension was added 1.0 g acetobromo- $\alpha$ -D-glucose and heated for 2 h at 60°, then filtered through a bed of silica gel and eluted with dichloromethane and methanol. The yellow eluent was concentrated under vacuum to obtain yellowish crystals. Proton NMR spectrum showed the crystals were consisted of 2 possible monoglucosides and a doubly glycosylated product.

REFERENCE COUNT:

THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1999:440767 CAPLUS Full-text

DOCUMENT NUMBER:

131:228604

TITLE:

Synergistic methodologies for the synthesis of 3-aroyl-2-arylbenzo[b]thiophene-based selective

estrogen receptor modulators. Two concise syntheses of

raloxifene

AUTHOR (S):

Bradley, David A.; Godfrey, Alexander G.; Schmid,

Christopher R.

CORPORATE SOURCE:

Chemical Process Research and Development, A Division

of Eli Lilly and Company, Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN,

46285-4813, USA

SOURCE: Tetrahedron Letters (1999), 40(28), 5155-5159

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal LANGUAGE: English

AB Functionalized benzo[b]thiophene intermediates are prepd. which allow fully independent elaboration of the 2-aryl position or the tether position of benzo[b]thiophene-based selective estrogen receptor modulators (SERMs). Two

concise syntheses of the SERM raloxifene (Evista) are presented.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1999:188589 CAPLUS Full-text

DOCUMENT NUMBER: 130:311683

TITLE: Novel nonsteroidal selective estrogen receptor

modulators. Carbon and heteroatom replacement of oxygen in the ethoxypiperidine region of raloxifene

AUTHOR(S): Schmid, Christopher R.; Sluka, James P.; Duke, Kristen

M.; Glasebrook, Andrew W.

CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly

and Company, Lilly Corporate Center, Indianapolis, IN,

46285, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (1999), 9(4),

523-528

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal LANGUAGE: English

AB Compds. were synthesized where oxygen in the ethoxypiperidine region of raloxifene is replaced with carbon, sulfur, or nitrogen linkages. Thia- and aza-substituted compds. were prepared by novel methodol. The compds. were evaluated in vitro as selective estrogen receptor modulators (SERMs). Calcns. suggested the compds. exhibit an ER-α binding affinity/conformational energy relationship.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1999:71534 CAPLUS Full-text

DOCUMENT NUMBER: 130:196550

TITLE: Nucleophilic aromatic substitution on

3-aroyl-2-arylbenzothiophenes. Rapid access to raloxifene and other selective estrogen receptor

modulators

AUTHOR(S): Schmid, Christopher R.; Sluka, James P.; Duke, Kristin

Μ.

CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly

and Company, Lilly Corporate Center, Indianapolis, IN,

46285-4813, USA

SOURCE: Tetrahedron Letters (1999), 40(4), 675-678

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal LANGUAGE: English

OTHER SOURCE(S): CASREACT 130:196550

AB Versatile, mild and high yielding methods for nucleophilic arom. substitution of 2-dialkylamino-1-ethoxides and related nucleophiles on 3-aroyl-2-arylbenzothiophene nuclei are presented. A short synthesis of raloxifene is detailed.

REFERENCE COUNT:

THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1998:721690 CAPLUS Full-text

DOCUMENT NUMBER:

130:3769

TITLE:

Processes for preparing benzothiophenes

INVENTOR(S):

McGill, John McNeil, III; Misner, Jerry Wayne; Zhang,

Tony Yantao

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA PCT Int. Appl., 26 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

SOURCE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

P	AT											LICAT					ATE	
-							-									-		
W	O	9849	156			<b>A1</b>		1998	1105		WO :	1998-	US85	09		1	9980	428
		W:	AL,	AM,	AU,	AZ,	BA,	BB,	BG,	BR,	BY	, CA,	CN,	CU,	CZ,	EE,	GE,	GH,
			GM,	GW,	HU,	ID,	IL,	IS,	ĴΡ,	KE,	KG	, KP,	KR,	KZ,	LC,	LK,	LR,	LS,
			LT,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO	, NZ,	PL,	RO,	RU,	SD,	SG,	SI,
			SK,	SL,	TJ,	TM,	TR,	TT,	UA,	UG,	US,	, UZ,	VN,	YU,	ZW			
		RW:	GH,	GM,	ΚĒ,	LS,	MW,	SD,	SZ,	ŪĠ,	ZW	, BF,	ВJ,	CF,	CG,	CI,	CM,	GA,
			GN,	ML,	MR,	NE,	SN,	TD,	TG									
C	Α	2287	943			A1		1998	1105		CA :	1998-	2287	943		1	9980	428
A	U.	9872	613			Α		1998	1124		AU :	1998-	7261	3		1	9980	428
В	R	98094	439			Α		2000	0613		BR :	1998-	9439			1	9980	428
H	U.	2000	0318'	7		, A2		2001	0528		HU 2	2000-	3187			1	9980	428
J	P	2001	5223′	72		T		2001	1113		JP :	1998-	5472	77 <sub>.</sub>		1	9980	428
U	S	6090	949			Α		2000	0718	•	US :	1998-	6949	7		1	9980	429
E	P	8755	10			<b>A1</b>		1998	1104		EP :	1998-	3033	74		1	9980	430
		R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	, IT,	LI,	LU,	NL,	SE,	MC,	PT,
			•	•		LV,												
								2000	0331		MX :	1999-	9883			1	9991	
PRIORI	ΤY	APP	LN.	INFO	. :		•			•	US :	1997-	4517	7P	•	P 1	9970	430
										1	WO :	1998-	US85	09	,	W 1	9980	428
OTHER	SO	URCE	(S):			CASI	REAC	T 13	0:37	69;	MARI	PAT 1	30:3	769				
GT																		

#### \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. [I; Y = Cl, Br, I, SO2(C1-4 alkyl), etc.] were prepd. by reacting benzo[b]thiophene II [R51, R52 = hydroxy protecting groups] with benzoyl chloride III [R8 = acyl activating group] in the presence of a boron trihalide such as BCl3. Compds. I were reacted further with an amine HNR6R7 [R6, R7 = C1-4 alkyl; NR6R7 = piperidino, pyrrolidino, morpholino, etc.] to produce benzothiophenes IV and their salts.

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER:

1998:721501 CAPLUS Full-text

DOCUMENT NUMBER:

130:3768

TITLE:

Demethylation process for preparing benzo[b]thiophenes

INVENTOR(S):

Hoard, David Warren; Luke, Wayne Douglas

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

Eur. Pat. Appl., 13 pp.

GI

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.		KIND	DATE	APPLICATION NO.		DATE
EP 875511		<b>A1</b>	19981104	EP 1998-303345		19980429
R: AT,	BE, CH,	DE,	DK, ES, FR,	GB, GR, IT, LI, LU,	NL,	SE, MC, PT,
IE,	SI, LT,	LV,	FI, RO			
CA 2236254		A1	19981030	CA 1998-2236254		19980427
JP 11005789	•	A	19990112	JP 1998-118628		19980428
US 5994547	•	Α	19991130	US 1998-69500		19980429
PRIORITY APPLN.	INFO.:			US 1997-45156P	P	19970430
OTHER SOURCE(S):		CASR	EACT 130:376	68; MARPAT 130:3768		
GT						

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

The prepn. of benzo[b] thiophenes I [R1, R2 = C1-4 alkyl; NR1R2 = piperidino, AΒ pyrrolidino, etc.] by the acylation of alkoxy protected starting materials followed by demethylation of II using essentially odorless thiol compound (2methyl-5-t-Bu-benzenethiol) are provided herewith. Demethylation may be . carried out in the same reaction vessel without isolation of the acylated, protected material.

II

REFERENCE COUNT:

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 20 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1998:719257 CAPLUS Full-text

10

DOCUMENT NUMBER:

130:3765

TITLE:

Intermediates and processes for preparing

benzo[b] thiophenes

INVENTOR(S):

SOURCE:

LANGUAGE:

Misner, Jerry Wayne; Schmid, Christopher Randall

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA PCT Int. Appl., 59 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	TENT 1		KIN	D :	DATE			APP	LICAT	ION 1	NO.		D	ATE			
WO	9848	793			A1	-	 1998:	1105		wo	 1998-	US85	10		1	9980	428
,	W:	AL,	AM,	AT,	ĂU,	ΑZ,	BA,	BB,	ВG,	BR	, BY,	CA,	CH,	CN,	CU,	CZ,	DE,
-		DK,	EE,	ES,	FI,	GB,	GE,	GH,	GM,	GW	, HU,	ID,	IL,	IS,	JP,	ΚE,	KG,
		KP,	KR,	KZ,	LC,	LK,	LR,	LS,	LT,	LU	, LV,	MD,	MG,	MK,	MN,	MW,	MX,
		NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG	, SI;	SK,	SL,	TJ,	TM,	TR,	TT,
		UA,	UG,	US,	UZ,	VN,	YU,	ZW									
	RW:	GH,	GM,	KE,	LS,	MW,	SD,	SZ,	ŪĠ,	ZW	, AT,	BE,	CH,	CY,	DE,	DK,	ES,
		FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL	, PT,	SE,	BF,	ВJ,	CF,	CG,	CI,
		CM,	GΑ,	GN,	ML,	MR,	NE,	SN,	TD,	TG							
CA	2287	922			<b>A1</b>		1998:	1105		CA	1998-	2287	922		1	9980	428
AU	9872	614			Α		1998:	1124		ΑU	1998-	7261	4		1	9980	428
EP	9790	76			<b>A1</b>		2000	0216		ΕP	1998-	9199	36		1	9980	428
	R:	AT,	BE,	DE,	DK,	ES,	FR,	GB,	GR,	IT	, NL,	SE,	PT,	ΙE,	FΙ		
JP	2001	5232	53		T		2001	1120	1	JP	1998-	5472	78		1	9980	428
US	6018	056			Α		2000	0125		US ·	1998-	6927	8		1	9980	429
PRIORIT	Y APP	LN.	INFO	. :					•	US	1997-	4513	1P	:	P 1	9970	430
										WO	1998-	US85	10	1	W 1	9980	428
OTHER S	OURCE	(S):			CASI	REAC	Т 13	0:37	65;	MAR	PAT 1	30:3	765				•

# \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. [I-III; R = hydroxy protecting group; Y = CO2H, CO2(C1-4 alkyl), C(halo), etc.; A = OH, halo, NO2, etc.; R1 = hydroxy protecting group, H], useful intermediates in the further preparation of pharmaceutical benzo[b]thiophenes, were prepared Thus, reaction of 6-methoxythianaphthen-2one with p-anisaldehyde in the presence of piperidine in EtOH and THF afforded 45% E/Z-I [R = Me].

REFERENCE COUNT:

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 21 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1998:161136 CAPLUS Full-text

DOCUMENT NUMBER:

128:221639

TITLE:

Preparation of amorphous benzothiophenes for

pharmaceuticals

INVENTOR(S):

Cuff, George W.; Thakkar, Arvind L.

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA; Cuff, George W.; Thakkar,

Arvind L.

SOURCE:

PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PAT	CENT 1						DATE	•	A	PP	LICA	LION	NO.		Ι	ATE	
 ₩0	9808				 A1		1998	0305	- W	0	1997	 -US14	768		1	.9970	 822
					AZ,												
					JP,												
					MX,												
					ŪĠ,												
	RW:				MW,							CF,	CG,	CI,	CM,	GA,	GN,
					SN,												
EP	8266	82	·	·	A1	·	1998	0304	E	P	1997	-3064	26		1	9970	822
EP	8266	82.			B1		2003	0312									
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT	, LI,	LU,	NL,	SE,	MC,	PT,
					LV,						•						
CA	2263	175	•		A1		1998	0305	С	A	1997	-2263	175		. 1	9970	822
AU	9742	335			Α.		1998	0319	Α	U	1997	-4233	5		1	9970	822
AU	7239	87			B2		2000	0907									
IN	1829	40			A1		1999	0814	I	N	1997	-CA15	49		1	.9970	822
BR	9713	176			Α		2000	0208	В	R	1997	-1317	6		1	.9970	822
CN	1244	124			Α		2000	0209	C	N	1997	-1974	34		1	.9970	822
HU	2000	0117	2		A2		2001	0628	Н	U	2000	-1172			1	.9970	822
HU	2000	0117	2		<b>A3</b>		2002	0128									
NZ	3338	39			A		2001	0629	N	Z	1997	-3338	39		1	.9970	822
IL	1286	41			Α		2001	1031	I	L	1997	-1286	41		1	9970	822
	9900				T2		2002	0121	Т	'R	1999	-403			1	.9970	822
JP	2002	5141	74		T		2002	0514		_		-5117				9970	822
AT	2342	95			T		2003	0315	A	Ţ	1997	-3064	26		3	9970	822
ES	2195	089 -			Т3		2003	1201	E	S	1997	-3064	26		1	9970	822
ZA	9707	617			Α		1999	0225	Z	Α	1997	-7617			1	9970	825
US	6713	494			B1		2004	0330	บ	S	1997	-9187	41		1	9970	825
NO	9900	914			Α		1999	0225		-		-914			1	9990	225
KR	2000	0359	41		A.		2000	0626				-7016				9990	
RIORIT	APP	LN.	INFO	.:					U	S	1996	-2483	1P	1	P 1	9960	828
				•					W	O	1997	-US14	768	1	W 1	9970	822
שששים כנ	איזופריבי	101.			MADD	ъπ	128.	2216	3 9								

OTHER SOURCE(S): MARPAT 128:221639

AB A method for prepg. an amorphous form of a benzothiophene such as raloxifene is described. Thus, raloxifene-HCl was prepared by a series of reactions starting from 3-methoxybenzenethiol and 4'-methoxyphenacyl bromide. A formulation contained PEG-1450 70, spray-dried lactose 1.5, colloidal SiO2 1.5, Polysorbate-80 2.0, and raloxifene-HCl 25%. The bioavailability of raloxifene-HCl and the pharmacol. effects of this compound on osteoporosis and hyperlipidemia were determined

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1997:589698 CAPLUS Full-text

DOCUMENT NUMBER:

127:272904

TITLE:

Evaluation of piperidinoethoxy moiety as an antiestrogenic substituent in non-steroidal

anti-estrogens: fertility regulation

AUTHOR(S): Tripathi, Sachi; Dwivedy, Indra; Dhar, J. D.; Dwivedy,

Anila; Ray, Suprabhat

CORPORATE SOURCE:

Medicinal Chemistry Division, Central Drug Research

Institute, Lucknow, 226 001, India

SOURCE:

Bioorganic & Medicinal Chemistry Letters (1997),

7(16), 2131-2136

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER:
DOCUMENT TYPE:

Elsevier Journal

English LANGUAGE:

A piperidinoethoxy substituent in non-steroidal antiestrogens has a relatively AB higher antiestrogenic effect as compared to a pyrrolidinoethoxy moiety. However, the antagonistic activity is more depended on the mol. geometry than the nature of the basic chain. No significant difference in the antifertility activity in these two sets of compds. was observed

REFERENCE COUNT:

12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 23 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1997:124440 CAPLUS Full-text

DOCUMENT NUMBER:

126:144105

TITLE:

Preparation of 3-phenylbenzo[b]thiophenes

INVENTOR (S):

Hoard, David W.; Luke, Wayne D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA; Hoard, David W.; Luke, Wayne

APPLICATION NO.

DATE

SOURCE:

PCT Int. Appl., 50 pp.

DATE

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

KIND

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.

PA	IENI I									AFF			NO.		_			
WO	9640									WO	1996	-US94	77			199	606	504
	W:	AL,	AM,	AT,	AU,	AZ,	BB,	BG,	BR,	BY	, CA	, CH,	CN,	CZ,	DE	c, D	K,	EE,
		ES,	FI,	GB,	GE,	HU,	IL,	IS,	JP,	KE	, KG	, KP,	KR,	ΚZ,	LF	(, L	R,	LS,
		LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX	, NO	, NZ,	PL,	PT,	RC	), R	U,	SD,
		SE,	SG															
	RW:	ΚE,	LS,	MW,	SD,	SZ,	UG,	AT,	BE,	CH	, DE	, DK,	ES,	FI,	FF	≀, G	В,	GR,
		ΙE,	IT,									cG,				1		
US	5606	075			A		1997	0225		US	1995	-4810	15		•	199	506	507
CA	2223	709										-2223				199	606	504
AU	9661	010			Α		1996	1230		ΑU	1996	-6101	0			199	606	504
AU	7030	17																
EP	8303	55			A1		1998	0325		ΕP	1996	-9183	20			199	606	504
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT	', LI,	LU,	NL,	SE	E, F	Т,	IE,
		SI,	LT,	LV,	FI													
CN	1192	738			Α		1998	0909		CN	1996	-1961	09			199	606	504
BR	9608	851										-8851						
JP	1150	7347			T		1999	0629		JP	1996	-5017	87			199	606	504
HU	9900	898			A2		1999	0728		HU	1999	-898				199	606	504
	9900						2000											
EP	1092	714			A2		2001	0418		ΕP	2000	-1282	07			199	606	504
EP	1092																	
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT	', LI,	LU,	NL,	SE	, P	Т,	ΙE,
		SI,	LT,															
IL	1221	28			Α		2001	8080		ΙL	1996	-1221	28			199	606	504
					Α		1998	0127				-5627				199		
PRIORIT	Y APP	LN.	INFO	. :								-4810						
												-9183						
										WO	1996	-US94	77		W	199	606	504
OTHER S	OURCE	(S):			MARI	PAT	126:	1,441(	05									

GI

$$R^{1}$$
  $R^{2}$   $R^{2}$ 

Title compds. [I; R1, R2 = H, halo, (aryl)alkoxy; NH2] were pred. by AΒ cyclization of 4-R1C6H4CH:C(SR4)C6H4R2-4 [R4 = trialkylsilyloxy, (di) (alkyl) amino, alkylthio, etc.] in the presence of an acid.

ANSWER 24 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3

ACCESSION NUMBER:

1996:740256 CAPLUS Full-text

DOCUMENT NUMBER:

126:7985

TITLE:

Preparation of 3-[4-(2-heterocyclylethoxy)benzoyl-2-

phenylbenzothiophenes for use in alleviating the

symptoms of post-menopausal syndrome

INVENTOR(S):

Dodge, Jeffrey Alan; Jones, Charles David; Bourgeois,

Tokarz Michelle Lee

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 67 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	rent 1	NO.			KINI	D	DATE		Α	PPL	ICAT	ION 1	NO.		D.	ATE		
	7387: 7387:						1996 1997		E	P 1	996-	3027	13		1	9960	418	
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FI,	FR,	GB,	GR,	ΙE,	İT,	LI,	NL,	PT,	SE	
US	6608	090			B1		2003	0819	. ប	s 1	995-	4265	52		1	9950	421	
CA	2215	902			<b>A1</b>		1996	1024	C	'A 1	996-	2215	902		1	9960	418	
WO	9632	937			A1		1996	1024	W	0 1	996-1	US53	82		1	9960	418	
	W:	AL,	AM,	AU,	ΑZ,	BB,	BG,	BR,	BY,	CA,	CN,	CZ,	EE,	GE,	HU,	IS,	JP,	
		KE,	KG,	KP,	KR,	KZ,	LK,	LR,	LS,	LT,	LV,	MD,	MG,	MK,	MN,	MW.,	MX,	
		NO,	NZ,	PL,	RO,	RU,	SD,	SG,	SI,	SK,	ТJ,	TM,	TR,	TT,	UA,	UG,	US,	
		US,	UZ															
	RW:	KΕ,	LS,	MW,	SD,	SZ,	UG,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	ML,	MR,	
	·	NE,	SN,	TD,	TG													
AU	9655	549			Α		1996	1107	Α	U 1	996-	5554	9		1	9960	418	
JP	1150	4013			T		1999	0406	J	P 1	996-	5319	11		1	9960	418	
PRIORITY	Y APP	LN.	INFO	.:					U	S 1	995-	4263	39	1	A 1	9950	421	
									U	s 1	995-	4265	52	1	A 1	9950	421	
									W	0 1	996-1	US53	82	Ţ	1	9960	418	
OTHER SO	OURCE	(S):			MARI	PAT	126:	7985										

GI

$$\mathbb{R}^{1}$$
 $\mathbb{R}^{2}$ 
 $\mathbb{R}^{2}$ 

The title compds. [I; R1, R2 = H, OH, alkoxy, etc.; R3 = (substituted) pyrrolidino, piperidino, piperazino, etc.], useful in alleviating the symptoms of post-menopausal syndrome related to osteoporosis, cardiovascular disease, hyperlipidemia, estrogen-dependent cancer, and in alleviating the symptoms of uterine fibroid disease, endometriosis, aortal smooth muscle cell proliferation, and restenosis, were prepared and formulated. Thus, reaction of bromide II with 3-phenylpyrrolidine in DMF followed by demethylation with EtSH/AlCl3 in CH2Cl2 afforded I [R1, R2 = H; R3 = 3-Ph-pyrrolidin-1-yl] which reduced 63.4% serum cholesterol at 10 mg/kg.

L3 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:672963 CAPLUS Full-text

DOCUMENT NUMBER:

126:7983

TITLE:

Process for the synthesis of benzo[b]thiophenes

INVENTOR(S):

Hoard, David W.; Luke, Wayne D.

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

U.S., 10 pp.

DOCUMENT TYPE:

CODEN: USXXAM Patent

LANGUAGE:

racene Daallab

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

רמק	CENT 1	NO.			кти	ח	DATE		;	APPL	TCAT	ON :	NO.		D	ATE	
US	5569	772					1996	1029	1	JS 1	995-	4868	73		1:	9950	607
	2223															9960	604
WO	9640	678			A1		1996	1219		WO 1	996-1	US 93	57		1	9960	604
	W:	AL,	AM,	ΑT,	ΑU,	ΑZ,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CZ,	DE,	DK,	EE,
		ES,	FI,	GB,	GE,	HU,	IL,	IS,	JP,	KE,	KG,	KP,	KR,	ΚZ,	LK,	LR,	LS,
		LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,
		SE,	SG					,									
	RW:	KE,	LS,	MW,	SD,	SZ,	UG,	ΑT,	BE,	CH,	DE,	DK,	ES,	FI,	FR,	GB,	GR,
		ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA		
ΑU	9660	970			Α		1996	1230	7	AU 1	996-	6097	0		1	9960	604
ΑU	6985	58			B2		1998	1029									
ΕP	8303	56			A1		1998	0325	]	EP 1	996-	9182	77		1:	9960	604
EР	8303	56			B1		2001	0822									
1	· R ·	AT.	BE.	CH.	DE.	DK.	ES.	FR.	GB.	GR.	TT.	LI.	LU.	NL.	SE.	PT.	IE.

SI, LT, LV,	FΙ	•		•		•
CN 1192212	A	19980902	CN	1996-195899		19960604
BR 9609156	A	19990629	BR	1996-9156		19960604
JP 11507338	T	19990629	JP	1997-501694		19960604
HU 9900903	. A2	19990728	HU	1999-903		19960604
ни 9900903	<b>A</b> 3	20010129				
IL 122091	A	20010520	IL	1996-122091		19960604
AT 204575	T	20010915	ΑT	1996-918277		19960604
ES 2159742	T3	20011016	ES	1996-918277		19960604
PT 830356	T	20011228	PT	1996-918277		19960604
NO 9705579	Α	19971203	NO	1997-5579		19971203
PRIORITY APPLN. INFO.:			US	1995-486873	Α	19950607
			WO	1996-US9357	W	19960604
A = 11 = 1	~ ~ ~ ~	E3.00 106 5000				

OTHER SOURCE(S):

CASREACT 126:7983; MARPAT 126:7983

GI

$$R^{1}$$
 $R^{2}$ 
 $R^{2}$ 

AB The title compds. I [R1, R2 = H, alkoxy, etc.] are prepd. Thus, treatment of (E)-tert-Bu 4,4'-dimethoxystilbenyl sulfoxide with p-toluenesulfonic acid in refluxing toluene gave, after workup and purifn, (E)- and (Z)-I [R1 = R2 = MeO].

L3 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:649600 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

125:266032

TITLE:

Phosphorous-containing benzothiophenes, their preparation, their use in treating postmenopausal

syndrome-associated indications and estrogen-dependent

diseases, and pharmaceuticals containing them

INVENTOR(S):

Bryant, Henry U.; Dodge, Jeffrey A.; Nissen, Jeffrey

s.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 19 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 729964	A1	19960904	EP 1996-300878	19960209
EP 729964	B1	20010509		

R	: AT,	BE, C	H, DE,	DK, ES,	FR, G	B, GR	, IE,	IT,	LI,	LU,	NL,	PT,	SE
US 64	79517		B1	2002	1112	US	1995-	39594	4		1	9950	228
ES 21	58242		Т3	2001	0901	ES	1996-	30087	8		1	9960:	209
CA 21	69414		A1	1996	0829	CA	1996-	21694	14		1	9960	213
JP 08	259560		Α	1996	1008	JP	1996-	25281			1	9960:	213
US 59	98443		Α	1999	1207	US	1997-	94684	2		1	9971	800
PRIORITY A	PPLN.	INFO.:				US	1995-	39594	4	7	A 1	9950	228
OTHER SOUR	CE(S):		MARI	PAT 125:	266032								
GI													

Phosphorus-contg. benzothiophene compds. I [R1, R2 = H, OH, halo, OPO(O-alkyl)2, OPO(O-aryl)2, OPO(alkyl)2, OPO(aryl)2, OPO3-2, in which not more than one of R1 and R2 may be H, OH or halo; R3, R4 = CO(CH2)3, CO(CH2)4, alkyl, or R3 and R4 combine to form, with the nitrogen to which they are attached, piperidine, morpholine, pyrrolidine, 3-methylpyrrolidine, 3,3-dimethylpyrrolidine, 3,4-dimethylpyrrolidine, azepine, or pipecoline], and pharmaceutically acceptable salts thereof, are provided which are useful for the treatment of the various medical indications associated with postmenopausal syndrome, as well as estrogen-dependent diseases, including cancer of the breast, uterus and cervix. Also provided are intermediate compds. and processes useful for preparing the pharmaceutically active compds. of the invention, as well as pharmaceutical compns. containing compds. of the invention.

L3 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996

1996:333087 CAPLUS Full-text

DOCUMENT NUMBER:

125:86485

TITLE:

Prepn. of vinyl sulfenic acid derivatives for

benzo[b]thiophene synthesis

INVENTOR(S):

Hoard, David W.; Luke, Wayne D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 13 pp. CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5514826	Α	19960507	US 1995-483607	19950607
CA 2224225	A1	19961219	CA 1996-2224225	19960604
WO 9640693	<b>A1</b>	19961219	WO 1996-US9460	19960604

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM AU 9661003 Α 19961230 AU 1996-61003 19960604 AU 698076 B2 19981022 19980325 EP 1996-918314 19960604 EP 830362 A1 AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, R: SI, LT, LV, FI CN 1996-195947 19960604 Α 19980902 CN 1192215 CN 1068883 В 20010725 BR 9608847 Α 19990608 BR 1996-8847 19960604 JP 11507346 Т 19990629 JP 1997-501774 19960604 HU 1999-923 19960604 HU 9900923 A2 19990728 А3 20000228 HU 9900923 IL 122127 Α 20010520 IL 1996-122127 19960604 19980128 NO 1997-5633 19971204 NO 9705633 Α CN 2000-130796 20001212 20020109 CN 1330071 Α US 1995-482692 19950607 PRIORITY APPLN. INFO.: US-1995-483607 19950607 WO 1996-US9460 W 19960604

$$R^1$$
  $CH = C$   $R^2$ 

The present invention is directed to novel vinyl sulfenic acid derivs. I [R1, R2 = H, alkoxy, arylalkoxy, halo, amino; R4 = OSi(R3)3, NR5R6, SR8; R5and/or R6 = H, alkyl, arylalkyl, aryl, -(CH2)5-, -(CH2)4-, -(CH2)2O(CH2)2-, -(CH2)6-; R8 = alkyl, aryl, arylalkyl useful for the synthesis of benzo[b]thiophenes, in particular 2-arylbenzo[b]thiophenes. E.g., desoxyanisoin reacts with 2-methyl-2-propanethiol to give I [R1 = R2 = OMe; R4 = C(Me)3] which in turn cyclizes to 6-methoxy-2-(4- methoxyphenyl)benzo[b]thiophene.

L3 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:256454 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

124:289252

TITLE:

GI

Process for preparing benzoic acid derivative

intermediates and benzothiophene pharmaceutical agents

INVENTOR(S):

Kjell, Douglas Patton

Ι

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 16 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
		<b></b>		
EP 699673	<b>A</b> 1	19960306	EP 1995-306053	19950830

EP	6996	73			B1		1998	0422									
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IE,	IT,	LI,	LU,	NL	, PT	SE
US	5731	436			Α		1998	0324	U	S	1994-	2988	91			1994	831
IL	1150	91			Α		2000	0831	I	L	1995	-1150	91			19950	828
IL	1265	93			Α		2000	0831	I	L	1995	-1265	93			1995	828
CA	2157	235			<b>A1</b>		1996	0301	C	A	1995	-2157	235			19950	0830
FI	9504	068			Α		1996	0301	F	Ι	1995	-4068				1995	0830
HU	7313	6			A2		1996	0628	Н	U	1995	-2539				19950	0830
BR	9503	847			Α		1996	0917	В	R	1995	-3847				19950	0830
AT	1653	56			T		1998	0515	A	Т	1995	-3060	53			19950	0830
ES	2114	722			Т3		1998	0601	E	s	1995	-3060	53			19950	0830
JP	0811	9912			Α		1996	0514	J	P	1995	-2231	84			1995	831
US	5955	608	•		A		1999	0921	U	S	1998	-1676	1			19980	130
PRIORIT	Y. APP	LN.	INFO	.:					U	S	1994	-2988	91	Ž	A	19940	831
									· I	L	1995	-1150	91	i	A3	1995	828
		4 - 4															

OTHER SOURCE(S):

MARPAT 124:289252

GI

The present invention provides a novel process for prepg. a compd. of formula AB RO2C(p-C6H4)O(CH2)nNR1R2 [R = C1-C4 alkyl; R1, R2 = C1-C4 alkyl, or combine to form piperidinyl, pyrrolidinyl, methylpyrrolidino, dimethylpyrrolidino, morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; n = 2, 3; or a pharmaceutically acceptable salt thereof, comprising (a) condensing (C1-C4 alkyl) 4-hydroxybenzoate with ethylene carbonate or propylene carbonate in the presence of a condensation catalyst and a moderately polar, water immiscible solvent having a high b.p.; (b) reacting the product of step (a), a compound of formula RO2(p-C6H4)O(CH2)nOH [R and n are as defined above, with a leaving group donor]; and (c) reacting the product of step (b), a compound of formula RO2(p-C6H4)O(CH2)nX [R and n are as defined above; X = leaving group with a base selected from the group consisting of piperidine, pyrrolidine, methylpyrrolidine, dimethylpyrrolidine, morpholine, dimethylamine, diethylamine, and 1-hexamethyleneamine]. The product of the above process also is novel and is useful for the preparation of pharmaceutically active compds. of formula I, particularly via the following novel process [R = C1-C4 alkyl; R1 and R2 each are independently C1-C4 alkyl, or combine to form piperidinyl, pyrrolidinyl, methylpyrrolidino, dimethylpyrrolidino, morpholino, dimethylamino, diethylamino, of 1-hexamethyleneimino; n = 2, 3; or a pharmaceutically acceptable salt thereof, comprising (a) condensing (C1-C4 alkyl) 4-hydroxybenzoate with ethylene carbonate or propylene carbonate in the presence of a condensation catalyst and a moderately polar, water immiscible solvent having a high b.p.; (b) reacting the product of step (a), a compound of formula RO2C(p-C6H4)O(CH2)nOH [R and n are as defined above, with the leaving group donor]; (c) reacting the product of step (b), a compound of formula RO2C(p-C6H4)O(CH2)nX [R and n are as defined above; X = leaving group

with a base selected from the group consisting of piperidine, pyrrolidine, methylpyrrolidine, dimethylpyrrolidine, morpholine, dimethylamine, diethylamine, and 1-hexamethyleneimine]; (d) reacting the product of step (c) with a compound of formula II [R3 and R4 are as defined above], or a pharmaceutically acceptable salt thereof; (e) optionally removing the reaction product from step (d); and (f) optionally forming a salt of the reaction product from either step (d) or step (e).

L3 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:237478 CAPLUS Full-text

DOCUMENT NUMBER: 124:289249

TITLE: An improved process for preparing 3-(4-

aminoethoxybenzoyl)benzo[b]thiophenes

INVENTOR(S): Alt, Charles Arthur

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: Eur. Pat. Appl., 15 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

GI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 693488	A1	19960124	EP 1995-305085	19950720
EP 693488	B1	20010919		
R: AT, BE, CH,	DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU,	NL, PT, SE
US 5523416	A	19960604	US 1995-422294	19950414
HU 71596	A2	19960129	HU 1995-2176	19950719
AU 9525068	A	19960201	AU 1995-25068	19950719
AU 684181	B2	19971204		
ZA 9506031	Α	19970120	ZA 1995-6031	19950719
CA 2154319	<b>A</b> 1	19960123	CA 1995-2154319	19950720
FI 9503513	Α	19960123	FI 1995-3513	19950720
NO 9502891	A	19960123	NO 1995-2891	19950720
CN 1116624	A ·	19960214	CN 1995-109618	19950720
JP 08053440	Α	19960227	JP 1995-183923	19950720
IL 114684	Α	19990620	IL 1995-114684	19950720
AT 205842	T	20011015	AT 1995-305085	19950720
ES 2160668		20011116	ES 1995-305085	19950720
PT 693488	T	20020228	PT 1995-305085	19950720
BR 9503408	Α	19960227	BR 1995-3408	19950721
US 5512684	A	19960430	US 1995-512724	19950808
PRIORITY APPLN. INFO.:			US 1994-279456	A 19940722
			US 1995-422294	A1 19950414

OTHER SOURCE(S): CASREACT 124:289249; MARPAT 124:289249

RO S OR 
$$Q = 0$$
 OR  $Q = 0$  OR  $Q$ 

A process for prepg. 6-alkoxy-3-(4-alkoxyphenyl)benzo[b]thiophenes (I; A = H; AB R = same or different C1-6 alkyl) in good yield on a manufacturing scale without generating a thick, potentially yield-reducing, paste and thereby without mixing problems, involves intramol. cyclization of  $\alpha$ -(3alkoxyphenylthio)-4-alkoxyacetophenones (II; R = same as above). invention also provides methods for converting  $\alpha$ -(alkoxyphenylthio)-4alkoxyacetophenones I (A = H; R = same as above) into 6-hydroxy-2-(4hydroxyphenyl) -3-[4-(2- aminoethoxy)benzoyl]benzo[B]thiophenes I (A = Q, R = H; R5 = NR1R2; wherein R1, R2 = C1-4 alkyl, or R1R2 = C4-6 polymethylene or CH2CH2OCH2CH2) via acylation of a dialkoxy benzo[b]thiophene I (A = H; R = same as above) with an acylating agent R4-Q (R4 = C1, Br, an active ester, etc.; R5 = same as above) under Friedel-Crafts conditions. bromo-4-methoxyacetophenone was added portion-wise to a mixture of 100 g 4methoxybenzenethiol and 39 g KOH in 300 mL and denatured EtOH in a cooling and stirred for 10 min in the cooling bath and at ambient temperature for 3 h to give, after workup, 158 g  $\alpha$ -(3-methoxyphenylthio)-4- methoxyacetophenone. The latter compound (6.92 g) was added steadily over 1/2 h to a mixture of 41.5 g polyphosphoric acid and 13.8 g phosphoric acid and the reaction mixture was heated at 85° for 1.75 h and cooled to 50°, to give , after extraction with toluene and crystallization, the desired 6-isomer, I (A = H, R = Me) (69% yield). The latter compound (30 g) was heated with 90 g pyridine hydrochloride with stirring at 210° for 30 min to give, after workup, 25.5 g I (A = R = H), which (40 g) was acetylated by Ac2O in the presence of 4dimethylaminopyridine in pyridine to give 52.5 g I (A = H, R = Ac). This compound (20 q) was added to a solution of 4-(2-piperidinoethoxy)benzoyl chloride (prepared from 16.3 g of the benzoic acid derivative) in ClCH2CH2Cl and stirred vigorously, followed by adding 73.4 g AlCl3 over 3 min, and the resulting mixture was stirred for 1 h to give, after workup, the desired product I [A = Q (wherein R5 = piperidino), R = Ac] as an oil, which was saponified with a mixture of 275 mL MeOH and 55 mL 5 n aqueous NaOH under reflux to give 10.5 g the title compound I [A = Q, wherein R5 = piperidino, R = H].

L3 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1996:150242 CAPLUS Full-text

OCIMENT NUMBER 104.

DOCUMENT NUMBER: 124:202950

TITLE: Preparation of benzothiophene glucopyranosides as

antihyperlipidemics.

INVENTOR(S): Dodge, Jeffrey Alan; Frolik, Charles Alan; Lindstrom,

Terry Donald; Lugar, Charles Willis Iii; Staten,

Gilbert Stanley

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: Eur. Pat. Appl., 20 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

		DATE	APPLICATION NO.	
	A1		EP 1995-303265	19950516
EP 683170				
			GB, GR, IE, IT, LI, LU,	
			US 1995-404701	19950315
US 6723739	B1 ·	20040420	US 1995-405555	19950315
CA 2149501	A1	19951121	CA 1995-2149501	19950516
ZA 9503975	Α	19961118	ZA 1995-3975	19950516
AT 184880	T	19991015	AT 1995-303265	19950516
ES 2136799	Т3	19991201	ES 1995-303265	19950516
AU 9520121	Α	19951130	AU 1995-20121	19950517
AU 683734		19971120	•	
JP 07316180	Α	19951205	JP 1995-118338	19950517
FI 9502420	Α	19951121	FI 1995-2420	19950518
	Α	19951121	NO 1995-1954	19950518
NO 304686	B1	19990201		
CN 1116626	Α	19960214	CN 1995-106322	19950518
CN 1039013	В	19980708		
BR 9502079	Α	19960305	BR 1995-2079	19950518
HU 73788	A2	19960930	HU 1995-1466	19950518
HU 219335	B	20010328		
· IL 113780		19990620	IL 1995-113780	19950518
GR 3032142	<b>T</b> 3	20000427	GR 1999-403228	19991215
		20040826	US 2004-778865	20040212
PRIORITY APPLN. INFO.:			US 1994-246655 A	19940520
			US 1995-405555 A	
OMITTED COLUMNIA (C)	CACDEA	am 104 00	2050	

OTHER SOURCE(S):

CASREACT 124:202950

GI

AΒ

Raloxifene metabolites (I) and (II) and their hydrochloride salts were prepared Thus, I and II, prepared from 6-tert-butyldimethylsilylraloxifene and 4'-tert-butyldimethylsilylraloxifene and Me 1,2,3,4-O-tetraacetyl-Dglucopyranuronate, at 1.3 mg/kg in rats decreased serum cholesterol by 44.5% and 56.8%, resp. Drug formulations are given.

ANSWER 31 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3

ACCESSION NUMBER:

1996:123714 CAPLUS Full-text

DOCUMENT NUMBER:

124:155994 .

TITLE:

Pharmaceutical compositions containing

2-phenyl-3-aryoylbenzothiophenes for for inhibiting

APPLICATION NO.

DATE

bone loss and lowering serum cholesterol

INVENTOR(S):

Draper, Michael W.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA Can. Pat. Appl., 31 pp.

SOURCE:

CODEN: CPXXEB

DATE

DOCUMENT TYPE:

Patent

LANGUAGE:

English

KIND

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.

FF	TENT NO	<b>,</b> .		171141	,	DAIB		<b>A</b> .		DICKI	1014				DAID	
CA	214199	9		A1		1995	0903	C	 A	1995-	 2141	 999			19950	207
บร	547884	.7		Α		1995	1226	U	s	1994-	2050	12			19940	302
ZA	950097	6		Α		1996	0807	Z	Α	1995-	976				19950	207
NZ	314699	)		Α		2000	0728	N	Z	1995-	3146	99			19950	207
EF	674903	}		A1		1995	1004	E	P	1995-	3008	42			19950	210
	R: A	T, BE,	CH.	DE.	DK	. ES.	FR.	GB,	GR	IE,	IT.	LI,	LU.	Ν̈́Ι	PT.	SE
NC	950077	-		A			0904			1995-			,		19950	
	210002			C1			1227		IJ	1995-	1027	78			19950	
	215027			C1			0610		-	1996-					19950	
	951355			A			0907			1995-					19950	_
	702575			B2			0225		-			_				
	072678			A			1017	J	P	1995-	4176	9			19950	301
	281838	-		B2			1030		-							
	950078	_		A			1024	BI	R	1995-	784				19950	301
	111953						0403			1995-					19950	
	72638	•	•	A2			0528			1995-					19950	
	102919	32		A			1104		-	1998-		50			19950	
	103105			A			1124			1998-					19950	
	561016			A			0311			1995-					19950	
	564179			A			0624			1995-					19950	
	574751	_		A			0505	_	_	1997-					19970	
	39050	. •		E1			0328	-	-	2003-		-			20030	
	Y APPLN	TNFO						-	-	1994-	-		2		19940	
111201111			• •							1995-					19950	
			-						_	1995-		_			19950	
7 T) 7			., .,		,	-										

AB A method of inhibiting bone loss or resorption, or lowering serum cholesterol, comprises administering to a human in need thereof pharmaceutical compns. containing 2-phenyl-3-aryoylbenzothiophenes, salt or solvate thereof, in a low dosage amount Raloxifene (I) at 50-200 mg decreased LDL cholesterol in postmenopausal women and there was no changes in HDL cholesterol level. A capsule contained I 150, starch 150, starch flowable powder 397, and silicone fluid 350 3.0 mg.

ANSWER 32 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN L3 ACCESSION NUMBER:

1995:991025 CAPLUS Full-text

DOCUMENT NUMBER:

124:106673

Methods for lowering serum cholesterol

INVENTOR(S): Black, Larry J.; Bryant, Henry U.; Cullinan, George

J.; Kauffman, Raymond F.

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: U.S., 14 pp. Cont.-in-part of U.S. Ser. No. 995, 222,

abandoned.
CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

GI

English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

		•		
			APPLICATION NO.	DATE
US 5464845	A B	19951107		
			•	
RU 2123335		19981220	RU 1993-55026	19931213
ZA 9309427	Α		ZA 1993-9427	19931215
SK 279271		19980805		
IL 108042	A	19980104	IL 1993-108042	
CZ 283863	B6	19980617	CZ 1993-2790	19931216
HU 69686	A2	19950928	HU 1993-3676	19931220
HU 223342	Bl	20040628		
RO 113806	B1	19981130	RO 1993-1739	19931220
PL 177349	B1	19991029	PL 1993-301579	19931220
CA 2112017	A1	19940623	CA 1993-2112017	19931221
	С			
NO 9304740	A	19940623	NO 1993-4740	19931221
AU 9352578	Α	19940707	AU 1993-52578	19931221
AU 669235	B2	19960530		
BR 9305182	Α	19940816	BR 1993-5182	19931221
JP 06234632	Α	19940823	JP 1993-323825	19931222
JP 3197129	B2	20010813		
CN 1094042	$\mathbf{A}$	19941026	CN 1993-121277	19931222
CN 1043608	В	19990616	•	
AT 233559	T	20030315	AT 1993-310438	19931222
	Т3	20031101	ES 1993-310438	19931222
PRIORITY APPLN. INFO.:			US 1992-995222. B2	19921222
OTHER SOURCE(S):	MARPAT	124:106673		
- • - • ,				

$$\begin{array}{c|c} & \text{CO} & \text{OCH}_2\text{CH}_2\text{(CH}_2\text{)}_n\text{R}^2 \\ \\ \text{R}^{1} & \text{I} \end{array}$$

AB A method of lowering serum cholesterol levels comprising administering to a patient a serum cholesterol lowering amount of a compound I wherein n is 0, 1 or 2; R is hydroxyl, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R1 is hydrogen, hydroxyl, chloro, bromo, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R2 is a heterocyclic ring (pyrrolidino, piperidino, or hexamethyleneimino); or a pharmaceutically acceptable salt or solvate thereof. The tested compds. lowered LDL without significantly affecting primary sex targets.

L3 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1995:362913 CAPLUS Full-text

DOCUMENT NUMBER: 122:213884

TITLE: . A chemical probe for the estrogen receptor: synthesis

of the 3H-isotopomer of raloxifene

AUTHOR(S): Dodge, Jeffrey A.; Stocksdale, Mark G.; Jones, C.

David

CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals

(1995), 36(1), 43-9

CODEN: JLCRD4; ISSN: 0362-4803

PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Radiolabeled raloxifene (LY156758) was prepd. by tritium gas hydrogenolysis of a 3-aroyl bis-brominated precursor. The requisite halogenated intermediate

was accessed by regioselective aroylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene with 3,5-dibromo-4-[2-(1-

piperdinyl)ethoxy]benzoyl chloride. Selective deprotection of the aryl Me

ethers in the presence of the ethoxy side-chain followed by palladium

catalyzed halogen-tritum exchange provided the target compound with a specific activity of 30.1 Ci/mmol.

L3 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1994:700754 CAPLUS Full-text

DOCUMENT NUMBER: 121:300754

TITLE: [[(Alkylsulfonyl)oxy]benzo[b]thienyl]methanones and

[[(aminocarbonyl)oxy]benzo[b]thienyl]methanones

pharmaceuticals

INVENTOR(S): Black, Larry John; Bryant, Henry Uhlman; Cullinan,

George Joseph

PATENT ASSIGNEE(S): Eli Lilly and Co., USA SOURCE: Eur. Pat. Appl., 26 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PAT	TENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP	617030	A1	19940928	EP 1994-301871	19940316
ΕP	617030	B1	19990526	•	•
	R: AT, BE,	CH, DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU,	NL, PT, SE
US	5482949	A	19960109	US 1993-35121	19930319
$z_{A}$	9401786	A	19950914	ZA 1994-1786	19940314
CA	2119091	A1	19940920	CA 1994-2119091	19940315
NO	9400940	A	19940920	NO 1994-940	19940316
ΑU	9457863	A	19940922	AU 1994-57863	19940316
ΑU	670177	B2	19960704		
BR	9401183	Α.	19941101	BR 1994-1183	19940316
HU	70549	A2	19951030	HU 1994-774	19940316
ΑT	180479	T	19990615	AT 1994-301871	19940316
ES	2132339	Т3	19990816	ES 1994-301871	19940316
FI	9401262	A	19940920	FI 1994-1262	19940317
JP	06321937	A	19941122	JP 1994-47091	19940317

CN 1097420	Α	19950118	CN 1994-102910	19940317
US 5994371	Α	19991130	US 1995-392445	19950222
US 5599833 ·	Α	19970204	US 1996-588670	19960117
US 5605924	Α	19970225	US 1996-588663	19960117
US 5798351	A	19980825	US 1997-958535	19971027
PRIORITY APPLN. INFO.:			บร 1993-35121	A 19930319
			US 1995-392445	A3 19950222

OTHER SOURCE(S):

MARPAT 121:300754

GI

# \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The (4-alkoxybenzoyl)benzo[b]thiophene-6-sulfonates and (4-alkoxybenzoyl)benzo[b]thien-6-yl carbamates I (R = OH, alkoxysulfonyl, carbamoyl; R1 = H, OH, halo, etc.; R2 = pyrrolidino, piperidino, etc.; X = bond, methine) were disclosed as agents for inhibiting the loss of bone, lowering serum cholesterol levels and therapeutically treating hormone dependent mammalian breast and uterine carcinoma. A specifically claimed example compound is [6-[(pentylsulfonyl)oxy]-2-[4-[(pentylsulfonyl)oxy]phenyl]benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (II).

L3 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1984:448784 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

101:48784

TITLE:

Antiestrogens. 2. Structure-activity studies in a series of 3-aroyl-2-arylbenzo[b]thiophene derivatives leading to [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride (LY 156758), a remarkably effective estrogen antagonist with only minimal intrinsic

estrogenicity

AUTHOR (S):

Jones, Charles D.; Jevnikar, Mary G.; Pike, Andrew J.; Peters, Mary K.; Black, Larry J.; Thompson, Allen R.;

Falcone, Julie F.; Clemens, James A.

CORPORATE SOURCE:

Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE:

Journal of Medicinal Chemistry (1984), 27(8), 1057-66

CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE:

Journal

LANGUAGE:

English

GI

In an effort to prep. nonsteroidal antiestrogens demonstrating greater antagonism and less intrinsic estrogenicity than those currently available, a series of 3-aroyl-2-arylbenzo[b]thiophene derivs. was synthesized. These compds. were prepared by Friedel-Crafts aroylation of appropriate O-protected 2-arylbenzo[b]thiophene nuclei with basic side-chain-bearing benzoyl chlorides followed by removal of the protective groups to provide the desired compds. containing both hydroxyl and basic side-chain functionality. A particularly useful method for the cleavage of aryl methoxy ethers without removal of (dialkylamino) ethoxy side chain functionality elsewhere in the mol. was AlCl3/EtSH. The benzothiophene derivs. were tested for their ability to inhibit the growth-stimulating action of estradiol on the immature rat uterus. Seemingly minor changes in the side-chain amine moiety had profound effects on the ability of the compds. to antagonize estradiol. Analogs having basic side chains containing cyclic (pyrrolidine, piperidine, and hexamethyleneamine) moieties had less intrinsic estrogenicity and antagonized estradiol action more completely than their noncyclic counterparts. The most effective antiestrogen in the series, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (I) [84449-90-1], elicited a modest uterotropic activity that did not increase with increasing dose. In antagonism of estradiol, I exhibited a degree of inhibition surpassing that of tamoxifen at any dose tested. The new benzothiophene antiestrogen also had high affinity for rat uterine cytoplasmic estrogen receptor and was an inhibitor of the growth of DMBA-induced rat mammary tumors.

L3 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1984:156501 CAPLUS Full-text

DOCUMENT NUMBER:

100:156501

TITLE:

Antiestrogenic and antiandrogenic benzothiophenes

INVENTOR(S):

Jones, Charles D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 23 pp. Cont.-in-part of U.S. Ser. No. 246,335,

abandoned.

CODEN: USXXAM

DOCUMENT TYPE:

Patent English

LANGUAGE:

אר מודאידי. ק

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLIC	ATION NO.		DATE
US 4418068	. <b>A</b>	19831129	US 198	1-331042		19811216
ZA 8202247	Α	19831130	ZA 198	2-2247		19820401
PRIORITY APPLN. INFO.:			US 198	1-246335	A2	19810403
OTHER SOURCE(S):	CASRE	ACT 100:1565	01 <sup>.</sup>			
GI						

Antiandrogenic and antiestrogenic [(piperidinoethoxy)benzoyl]benzothiophen es AB I [R,R1 = H, R2CO; R2 = H, cycloalkyl, (un)substituted alkyl, Ph] were prepared Thus, 2-(4-hydroxyphenyl)benzo[b]thiophene-6-ol was esterified with MeSO2Cl and the diester subjected to Friedel-Crafts acylation with 4-(2piperidinoethoxy) benzoyl chloride to give I (R = R1 = MeSO2). This was saponified to give I (R = R1 = H) (II). Immature female rats administered 0.03 µg estradiol propionate (III) s.c. together with 3 mg II s.c. daily for 4 d had average uterus weight of 21.3 mg. Those given III alone had average uterus weight of 65.9 mg. I also were effective as antiandrogens and as mammary tumor inhibitors.

L3 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

CAPLUS Full-text 1983:71917

DOCUMENT NUMBER:

98:71917

TITLE:

Benzothiophene compounds

INVENTOR (S):

Jones, Charles David

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 107 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PAT	TENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP	62503	A1	19821013	EP 1982-301737	19820401
	R: BE, CH, DE,	FR, GB	, IT, LU, NL	, SE	
AU	8282265	Α	19821007	AU 1982-82265	19820401
AU	555658	B2	19861002		
GB	2097788	A	19821110	GB 1982-9680	19820401
GB	2097788	В	19850424		
JP	57181081	Α	19821108	JP 1982-56479	19820402
PRIORITY	Y APPLN. INFO.:			US 1981-246335 A	19810403
				US 1981-331045 A	19811216

GI

[(Aminoethoxy)benzoyl]benzothiophenes I (Z = CH2CH2CH2, CHMeCH2) were prepared, and limited the increase of uterine weight in rats treated with estradiol. Thus, treating II (R = Br) with 3-methylpyrrolidine in DMF containing KI gave II (R = 3-methyl-1-pyrrolidinyl) which was deprotected by NaOH to give I (Z = CHMeCH2).

L3 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1983:71916 CAPLUS Full-text

DOCUMENT NUMBER: 98:71916

TITLE: 3-(4-Aminoethoxybenzoyl)benzo[b]thiophenes

חאתה

INVENTOR(S): Jones, Charles David; Goettel, Mary Elizabeth

PATENT ASSIGNEE(S): Eli Lilly and Co., USA SOURCE: Eur. Pat. Appl., 59 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

DATENTE NO

PA'	FENT NO.		KIND		APPLICATION NO.	•	DATE
EP	62504		A1	19821013	EP 1982-301738		19820401
EP	62504		B1	19860102			
	R: AT,	BE,	CH, DE,	FR, GB, IT,	LU, NL, SE		
US	4358593		Α	19821109	US 1981-246334		19810403
IL	65378		A	19860228	IL 1982-65378		19820330
CA	1167037		A1	19840508	CA 1982-400300		19820331
GB	2097392		A	19821103	GB 1982-9679		19820401
GB	2097392		В	19850424			
DD	201793		. A5	19830810	DD 1982-238654		19820401
CS	227348		B2	19840416	CS 1982-2357		19820401
$\mathtt{PL}$	130867		B1	19840929	PL 1982-235752		19820401
AT	17243		T	19860115	AT 1982-301738		19820401
DK	8201512		A	19821004	DK 1982-1512		19820402
FI	8201160		Α	19821004	FI 1982-1160		19820402
JP	57183788		Α	19821112	JP 1982-56480		19820402
ES	511124		A1	19830616	ES 1982-511124		19820402
HU	28787		A2	19831228	HU 1982-1026		19820402
HU	191353		В	19870227			•
SU	1155157		A3	19850507	SU 1982-3417550	) ·	19820402
PRIORITY	Y APPLN.	INFO.	:	a a	US 1981-246334	A	19810403
					US 1981-246335	A	19810403
•					US 1981-331045	A	19811216
					EP 1982-301738	Α	19820401

OTHER SOURCE(S):

MARPAT 98:71916

GI

AB

Benzothiophenes I [R = H; R1 = COC6H4O(CH2)2NR2R3-4; R2 = R3 = alkyl; R2R3 = (CH2)4-6, (CH2)2O(CH2)2, etc.] were prepared by Friedel-Crafts acylation of I

(R = Ac, Bz, MeSO2; R1 = H) followed by hydrolysis of the ester groups. Thus, HSC6H4OMe-3 was treated with BrCH2COC6H4OMe-4 to give 3-MeOC6H4SCH2COC6H4OMe-4, which was cyclized with polyphosphoric acid to give I (R = Me, R1 = H). Demethylation of the latter followed by esterification with MeSO2Cl gave I (R = MeSO2, R1 = H; II). Friedel-Crafts acylation of 4 g II with 4-Me2N(CH2)2OC6H4COCl gave 6.2 g I [R = MeSO2, R1 = COC6H4O(CH2)2NMe2-4, III]. Hydrolysis of III gave I (R = H). I are estrogens, antiestrogens, and antiandrogens (no data).

=> file reg SINCE FILE COST IN U.S. DOLLARS TOTAL ENTRY SESSION FULL ESTIMATED COST 115.67 124.13 SINCE FILE TOTAL DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) ENTRY SESSION CA SUBSCRIBER PRICE -30.42 -30.42

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http://www.cas.org/support/stngen/stndoc/properties.html

=> s e4

L4

1 "RALOXIFENE HYDROCHLORIDE"/CN

=> d l4 1 ide

- L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
- RN 82640-04-8 REGISTRY
- ED Entered STN: 16 Nov 1984
- CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl] [4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride (1:1) (CA INDEX NAME)
  OTHER CA INDEX NAMES:
- CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride (9CI)
  OTHER NAMES:

CN Bonebay

CN Bontact

CN Evista

CN Fiona

CN Keoxifene hydrochloride

CN LY 156758

CN Ralofen

CN Raloxifene hydrochloride

CN Reloxafine

MF C28 H27 N O4 S . Cl H

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, EMBASE, HSDB\*, IMSPATENTS, IMSRESEARCH, IPA, MRCK\*, MSDS-OHS, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS\*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL (\*File contains numerically searchable property data)

CRN (84449-90-1)

## \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HCl

329 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
329 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus COST IN U.S. DOLLARS SINCE FILE TOTAL SESSION ENTRY FULL ESTIMATED COST 8.25 132.38 SINCE FILE TOTAL DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) ENTRY SESSION -30.42 CA SUBSCRIBER PRICE 0.00

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FILE COVERS 1907 - 21 Aug 2007 VOL 147 ISS 9 FILE LAST UPDATED: 20 Aug 2007 (20070820/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

## http://www.cas.org/infopolicy.html

=> s 14

L5 329 L4

=> d scan

L5 329 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN

CC 63-6 (Pharmaceuticals)

TI Preparation of raloxifene hydrochloride capsules and establishment of its quality control standard

ST raloxifene hydrochloride capsules dissoln quality control

IT Drug delivery systems

(capsules; preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

IT Dissolution

Quality control

(preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

IT 63-42-3, Lactose 9004-32-4, Carboxymethyl cellulose sodium 9004-34-6, Cellulose, biological studies

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

IT 82640-04-8, Raloxifene hydrochloride

RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of raloxifene hydrochloride capsules and establishment of quality control standard)

#### HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L5 329 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN

CC 2-4 (Mammalian Hormones)

Section cross-reference(s): 1

TI Effectiveness of combined GnRH analogue plus raloxifene administration in the treatment of uterine leiomyomas: a prospective, randomized, single-blind, placebo-controlled clinical trial

ST leuprolide acetate SERM raloxifene pelvic pain menorrhagia uterine leiomyomas

IT Human

(GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Intestine, disease

(constipation; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine

leiomyomas)

IT Menopause

(hot flash; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Uterus, neoplasm

(leiomyoma; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Menstrual disorder

(menorrhagia; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Body, anatomical

(pelvis, pain; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Menopause

(premenopause; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Estrogen receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (selective modulator of; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT Urinary system, disease

(urinary frequency; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT 74381-53-6, Leuprolide acetate

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (Enantone; GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

IT 82640-04-8, Raloxifene hydrochloride

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(GnRH analog (Enantone) plus raloxifene hydrochloride (Evista) effectiveness in treatment of premenopausal women with uterine leiomyomas)

#### HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

- L5 329 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN
- IC ICM C07D333-64

IT

ICS C07D333-56

- CC 27-9 (Heterocyclic Compounds (One Hetero Atom))
- TI Demethylation process for preparing benzo[b]thiophenes
- ST demethylation benzothiophene benzenethiol
- IT 63675-73-0P 63675-74-1P 84541-36-6P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (demethylation process for preparing benzo[b]thiophenes)

63676-25-5P **82640-04-8P** 84449-87-6P 84449-90-1P

215662-11-6P 215662-12-7P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(demethylation process for preparing benzo[b]thiophenes)

```
IT
     108-90-7, Chlorobenzene, uses
     RL: NUU (Other use, unclassified); USES (Uses)
        (demethylation process for preparing benzo[b]thiophenes)
ΙT
                7340-90-1 7446-70-0, Aluminum chloride, reactions
     15570-12-4, 3-Methoxybenzenethiol
                                         84449-80-9
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (demethylation process for preparing benzo[b]thiophenes)
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1
L5
      329 ANSWERS
                    CAPLUS COPYRIGHT 2007 ACS on STN
IC
     ICM A61K031-445
     ICS A61K031-40; A61K031-38
INCL 514324000
     63-6 (Pharmaceuticals)
CC
     Section cross-reference(s): 1
TI
     Methods of decreasing serum calcium levels
     benzoyl benzothiophene calcium blood decrease; raloxifene calcium blood
ST
     decrease-
ΙT
     82640-04-8, Raloxifene hydrochloride
                                            84449-90-1, Raloxifene
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
        (benzoylbenzothiophene derivs. for decreasing serum calcium levels)
     7440-70-2, Calcium, biological studies
IT
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
     (Biological study); PROC (Process)
        (benzoylbenzothiophene derivs. for decreasing serum calcium levels)
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1
                    CAPLUS COPYRIGHT 2007 ACS on STN
L5
      329 ANSWERS
     C12Q001-02
IC
INCL 435029000
     2-1 (Mammalian Hormones)
CC
     Cell culture for screening estrogen agonists and antagonists
TI
     estrogen agonist screening cell culture; antagonist estrogen screening
ST
     cell culture
IT
     Animal cell line
        (C7 MCF7-173, in screening of estrogen agonists/antagonists)
IT
     Estrogens
     RL: ANST (Analytical study)
        (agonists, cell culture method for screening of)
     Cell proliferation
IT
        (cells dependent on estrogens for, in screening of estrogen
        agonists/antagonists)
IT
     Charcoal
     RL: ANST (Analytical study)
        (dextran-, human serum stripped with, for maintaining medium in cell
        culture method for screening of estrogen agonists/antagonists)
IT
     Blood serum
        (fetal bovine, for maintaining medium in cell culture method for
        screening of estrogen agonists/antagonists)
IT
     Animal tissue culture
        (for estrogen agonist/antagonist screening)
IT
     Proteins, biological studies
     RL: BIOL (Biological study)
        (inhibitory to proliferation of estrogen-dependent cells in vitro, for
        cell culture method for screeing of estrogen agonists/antagonists)
     Estrogens
IT
```

RL: PRP (Properties)

(antiestrogens, cell culture method for screening of)

IT Mammary gland

(neoplasm, cells of, in screening of estrogen agonists/antagonists)

RL: ANST (Analytical study)

(agonists and antagonists of, cell culture method for screening of)

IT 9004-54-0, Dextran, biological studies

RL: BIOL (Biological study)

(charcoal-, human serum stripped with, for maintaining medium in cell culture method for screening of estrogen agonists/antagonists)

IT 10540-29-1, Tamoxifen 34816-55-2, Moxestrol 63676-25-5, LY117018 71794-60-0, 11 $\beta$ -Chloromethylestradiol 82640-04-8, LY156758

120382-04-9, RU39411 57-83-0, Progesterone, biological studies

RL: ANST (Analytical study)

(estrogen agonist/antagonist activity of, determination of, cell culture method

for)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> s 14/prep

329 L4

4449106 PREP/RL

L6 34 L4/PREP

(L4 (L) PREP/RL)

=> d 16 ibib abs 1-

YOU HAVE REQUESTED DATA FROM 34 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2007:265820 CAPLUS Full-text

DOCUMENT NUMBER:

146:448285

TITLE:

Benzothiophenes, formulations containing same, and

methods

INVENTOR(S):

Cullinan, George J.; Palkowitz, Alan D.

PATENT ASSIGNEE(S):

USA

SOURCE:

Hung. Pat. Appl., 40pp.

CODEN: HUXXCV

DOCUMENT TYPE:

Patent

LANGUAGE:

Hungarian

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
,				
HU 9901882	A2	20000228	HU 1999-1882	19970219
HU 9901882	<b>A3</b>	20000328		
PRIORITY APPLN. INFO.:			HU 1999-1882	19970219
OTHER SOURCE(S):	MARPAT	146:448285		

GI

$$\begin{array}{c|c}
 & \text{OCH}_2\text{CH}_2\text{N} = \mathbb{R}^3 \\
 & \text{R4}
\end{array}$$

AB Benzothiophene N-oxides I [R1 = H, OH, alkoxy, OCO2(alkyl or aryl), OCO(alkyl or aryl), etc.; R2 = R1, C1 or F; R3 and R4 = alkyl or combine to form polymethylene or morpholine; X = CH2, CHOH, O or CO], useful for the treatment or prevention of medical indications associated with post-menopausal syndrome and breast cancer, are prepared Thus, [2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was oxidized using 30% aqueous H2O2 to give I [R1 = R2 = OH, R3R4 = (CH2)5, X = CO]. I reduce serum cholesterol compared to ovariectomized rats and do not cause a large increase in the number of eosinophils observed in the stromal layer of the ovariectomized rat uteri. In an osteoporosis test, I prevent bone loss in a general, dose-dependent manner. I were active in the MCF-7 proliferation assay and inhibited growth of DMBA-induced mammary tumors. A tablet formulation comprises: I 2.5-1000, cellulose 200-650, silicon dioxide 10-650, and stearic acid 5-15 mg/tablet.

L6 ANSWER 2 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2006:958171 CAPLUS Full-text

DOCUMENT NUMBER:

147:9760

TITLE:

Synthesis of raloxifene hydrochloride

AUTHOR (S):

Song, Yan-ling; Zhao, Yan-fang; Meng, Yan-qiu; Gong,

Ping

CORPORATE SOURCE:

Shenyang Institute of Chemical Technology, Faculty of

Pharmaceutical-Engineering, Shenyang, 110142, Peop.

Rep. China

SOURCE:

Zhongguo Xinyao Zazhi (2005), 14(7), 882-884

CODEN: ZXZHA6; ISSN: 1003-3734

PUBLISHER:

Zhongguo Xinyao Zazhi Youxian Gongsi

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

AB The synthesis of raloxifene hydrochloride [i.e., [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methan one hydrochloride] is reported. The target compound was synthesized from 3-methoxybenzenethiol and 4-methoxy-α-bromo acetophenone via five steps, including substitution, cyclization, Friedel-Crafts reaction, di-Me reaction and salt formation. The structure of the target compound was confirmed by IR, 1H-NMR and MS. This synthetic route required mild conditions and provided an improved yield and was easily controlled.

L6 ANSWER 3 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:1257978 CAPLUS Full-text

DOCUMENT NUMBER:

144:135192

TITLE:

Manufacture of raloxifene-hydrochloride-containing medicines for treating bone fracture delayed union or

nonunion

INVENTOR(S):

Zhang, Jianhao; Huang, Haibo

PATENT ASSIGNEE(S):

Peop. Rep. China

SOURCE:

Faming Zhuanli Shenqing Gongkai Shuomingshu, 8 pp.

CODEN: CNXXEV

DOCUMENT TYPE:

Patent Chinese

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1615860	A	20050518	CN 2003-10113253	20031111
PRIORITY APPLN. INFO.:			CN 2003-10113253	20031111

AB The title medicines are manufd. from (by wt.) raloxifene hydrochloride (35-45%) as effective components, diluent (50-60%), disintegrant (2-4%), lubricant (0.5-1%), and adhesive (2-3%). The medicines can be produced into various drug forms such as tablets, capsules, suspensions, powders, granules, solns., etc., and have advantages of short course of treatment, high recovery rate, etc.

ANSWER 4 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:547361 CAPLUS Full-text

DOCUMENT NUMBER:

143:59836

TITLE:

A process for preparing benzoic acid derivatives, useful as intermediates for preparation of raloxifene

Luke, Wayne Douglas

INVENTOR(S): PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

U.S. Pat. Appl. Publ., 10 pp.

CODEN: USXXCO

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005137396	A1	20050623	US 2003-745188	20031222
US 7012153	B2	20060314		
PRIORITY APPLN. INFO.:			US 2003-745188	20031222
OTHER SOURCE(S):	CASREA	CT 143:59836	; MARPAT 143:59836	

The invention relates to a prepn. of benzoic acid derivs. of formula RO2C-p-C6H4-O(CH2)2-3N(R1)R2 [wherein: R is alkyl; R1 and R2 are independently alkyl, or combined together with the nitrogen atom form piperidinyl, pyrrolidinyl, or morpholinyl, etc.], useful as intermediates for preparation of raloxifene. For instance, 4-[2-(piperidin-1-yl)ethoxy]benzoic acid hydrochloride was prepared via etherification of Me 4-hydroxybenzoate by 1-( $\beta$ chloroethyl)piperidine hydrochloride and subsequet hydrolysis with a yield of

99.2%. REFERENCE COUNT:

9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 5 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:29327 CAPLUS Full-text

DOCUMENT NUMBER:

142:134465

TITLE:

Process for preparing raloxifene hydrochloride

INVENTOR(S):

Ferrari, Massimo; Zinetti, Fabrizio; Belotti, Paolo

PATENT ASSIGNEE(S):

Erregierre S.p.A., Italy

SOURCE:

PCT Int. Appl., 19 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

#### PATENT INFORMATION:

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KIND
                                DATE
                                            APPLICATION NO.
                                                                    DATE
     PATENT NO.
                         ----
                          A1
                                20050113
                                            WO 2004-EP51263
                                                                    20040628
     WO 2005003116
            AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
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             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     CA 2549354
                          A1
                                20050113
                                            CA 2004-2549354
                                                                    20040628
     EP 1641773
                          A1
                                20060405
                                            EP 2004-741907
                                                                    20040628
           AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK
     US 2007100147
                          A1
                                20070503
                                            US 2005-562762
                                                                    20051227
PRIORITY APPLN. INFO.:
                                            IT 2003-MI1333
                                                                A 20030630
                                            WO 2004-EP51263
                                                                 W 20040628
```

OTHER SOURCE(S): CASREACT 142:134465

A process for prepg. raloxifene hydrochloride with a purity greater than 98% and low aluminum content comprises the following stages : (a) demethylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene in pyridine and hydrochloric acid to obtain 6-hydroxy-2-(4- hydroxyphenyl)benzo[b]thiophene in pyridine hydrochloride, (b) acetylation of 6-hydroxy-2-(4hydroxyphonyl)benzo[b]thiophene with an acetylating agent to obtain the corresponding 6-acetoxy-2-(4- acetoxyphenyl)benzo[b]thiophene (I), (c) acylation of 6-acetoxy-2-(4- acetoxyphonyl)benzo[b]thiophene with 4-(2piperidinoethoxy) benzoylchloride hydrochloride with aluminum trichloride in a halogenated solvent to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl] - benzo[b]thiophene, (d) hydrolysis of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene according to the following operating conditions: (d1) treatment of 6-acetoxy-2-(4-acetoxyphonyl)-3-[4- (2-piperidinoethoxy)benzoyl]benzo[b]thiophene with alkaline hydroxide in alc. solvent, (d2) acidification of the product obtained in the preceding stage (d1) with a strong acid, to obtain the corresponding raloxifene salt with the strong acid, characterized in that the strong acid used in stage (d2) is concentrated hydrochloric acid. Thus, thionyl chloride was added to a mixture of 4-(2-piperidinoethoxy) benzoic acid HCl salt and pyridine in refluxing methylene chloride; the mixture was stirred for 1 h and the solvent was distilled off; the mixture was cooled to 20°C, and I was The resulting mixture was mixed with aluminum trichloride in methylene chloride at 15°C to 30°C; the mixture was stirred for 1 h and was worked up : the product was treated with sodium hydroxide in methanol; water, Et acetate, and HCl were added; the suspension was centrifuged to give crude raloxifene hydrochloride.

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:617920 CAPLUS Full-text

DOCUMENT NUMBER: 142:463529

TITLE: Synthesis of raloxifene hydrochloride AUTHOR(S): Gong, Ping; Zhao, Yanfang; Wang, Dun

CORPORATE SOURCE: School of Pharmaceutical Engineering, Shenyang
Pharmaceutical University, Shenyang, 110016, Peop.

Rep. China

SOURCE:

Shenyang Yaoke Daxue Xuebao (2003), 20(2), 111-113

CODEN: SYDXFF; ISSN: 1006-2858

PUBLISHER:

Shenyang Yaoke Daxue Xuebao Bianjibu

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

OTHER SOURCE(S):

CASREACT 142:463529

Raloxifene hydrochloride, which is a selective estrogen receptor modulator, was synthesized from 3-methoxybenzenethiol and 2-bromo- 4'-methoxyacetophenone by etherification, cyclization in the presence of polyphosphoric acid, hydrolysis with HBr/HOAc to obtain 6-hydroxy- 2-(4hydroxyphenyl) benzothiophene, acylation with acetic anhydride, acylation with 4-[2-(1-piperidinyl)ethoxy]benzoyl chloride in the presence of AlCl3, saponification with 5M NaOH solution in methanol, and saltification with HCl. The overall yield was 10.0%, and its structure was confirmed by MS, 1H NMR,

ANSWER 7 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

13C NMR.

2002:348716 CAPLUS Full-text

DOCUMENT NUMBER:

138:137104

TITLE:

Synthesis of Raloxifene hydrochloride as selective

estrogen receptor modulator

AUTHOR(S):

Chen, Yanzhong; Liu, Yingxiang

CORPORATE SOURCE:

Guangdong College of Pharmacy, Canton, 510224, Peop.

Rep. China

SOURCE:

Guangdong Yaoxueyuan Xuebao (2002), 18(1), 1-3, 20

CODEN: GYXUF8

PUBLISHER:

Guangdong Yaoxueyuan

DOCUMENT TYPE:

Journal

LANGUAGE:

Chinese

OTHER SOURCE(S):

CASREACT 138:137104

Raloxifene was synthesized from α-bromo-p-methoxyacetophenone and mmethoxybenzenethiol via condensation, cyclization, acylation, and demethylation with the overall yield 49.2%. The chemical structure of compound was confirmed by 1H NMR, MS, IR, and elementary anal. The reaction conditions were mild and starting materials were com. available.

ANSWER 8 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2001:247325 CAPLUS Full-text

DOCUMENT NUMBER:

134:266100

TITLE:

Synthesis of 4-[(2-piperidin-1-yl)ethoxy]benzoic acid

for manufacture of Raloxifene hydrochloride

INVENTOR(S):

Luke, Wayne Douglas

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

PCT Int. Appl., 32 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

P.	PATENT NO.				KIN	D :	DATE			APPL	ICAT:	ION	NO.		D	ATE		
						-									-			
WC	2001	0233		A2		2001	0405	,	WO 2	000-1	US21	974	,	2	0000	918		
	W:	ΑE,	AG,	AL,	AM,	AT,	ΑU,	AZ,	BA,	BB,	BG,	BR,	BY,	ΒZ,	CA,	CH,	CN,	
		CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,	HR,	
		ΗU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	ΚP,	KR,	ΚZ,	LC,	LK,	LR,	LS,	LT,	
		LU.	LV.	MA.	MD.	MG.	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PL,	PT,	RO,	RU,	

SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

20020710 EP 2000-966691 20000918 EP 1220847 Α2

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, SI, LT, LV, FI, RO, MK, CY, AL

T· 20030318 JP 2001-526522 20000918 JP 2003510313 P 19990927

PRIORITY APPLN. INFO .: US 1999-156205P

WO 2000-US21974 W 20000918

CASREACT 134:266100; MARPAT 134:266100 OTHER SOURCE(S):

An improved process for the prepn. of 4[(2-piperidin-1-yl)ethoxy]benzoic acid derivs. comprises reacting haloalkyl amine X(CH2)nNR1R2 (X = halogen; R1, R2 = C1-4 alkyl, combined with nitrogen atom to form piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, 1-hexamethyleneimino group; n = 2, 3) with C1-6 alkyl p-hydroxybenzoate in the presence of a hydrated inorg. base in an appropriate solvent.

ANSWER 9 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1999:12339 CAPLUS Full-text

DOCUMENT NUMBER:

130:66385

TITLE:

Process for preparing benzoic acid derivatives as

intermediates in the synthesis of benzothiophenes

INVENTOR(S):

Chelius, Erik Christopher

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

U.S., 7 pp. CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

29

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
				-	
US 5852193	A	19981222	US 1998-69277		19980429
US 6075146	Α	20000613	US 1998-123889		19980728
PRIORITY APPLN. INFO.:		•	US 1997-45162P	P	19970430
			US 1998-69277	<b>A3</b>	19980429
OTHER SOURCE(S):	CASRE	ACT 130:66385	5; MARPAT 130:66385		

#### \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The title compds. [I; R1, R2 = C1-4 alkyl; NR1R2 = piperidino, pyrrolidino, AB morpholino, etc.; n = 2-3; R6 = carboxy protecting group] were prepared byreacting a hydroxylamine HO(CH2)nNR1R2 with a compound selected from W2O and W-halo (wherein W = p-toluenesulfonyl, methylsulfonyl, trifluoromethylsulfonyl, etc.) followed by reaction of the resulting Y1(CH2)nNR1R2 (Y1 = p-toluenesulfonyloxy, methylsulfonyloxy, trifluoromethylsulfonyloxy, etc.) with a compound II. Compds. I can be then reacted with benzothiophenes III (R4, R5 = hydroxy protecting groups) to afford compds. IV (R4, R5 = , H, hydroxy protecting groups) (example of such reaction was given).

REFERENCE COUNT:

THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CAPLUS COPYRIGHT 2007 ACS on STN L6 ANSWER 10 OF 34 ACCESSION NUMBER:

DOCUMENT NUMBER:

1998:721690 CAPLUS Full-text

130:3769

TITLE:

Processes for preparing benzothiophenes

INVENTOR(S):

McGill, John McNeil, III; Misner, Jerry Wayne; Zhang,

Tony Yantao

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

PCT Int. Appl., 26 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION: .

PA'	TENT	NO.			KIN	D	DATE			APP	LICA	rion	NO.		D	ATE	
WO	9849	 156			A1	_	1998	1105		WO	1998	-US85	09		1	9980	428
•	W:	AL,	AM,	AU,	ΑZ,	BA,	BB,	ВG,	BR,	BY	, CA	CN,	CU,	CZ,	EE,	GE,	GH,
		GM,	GW,	HU,	ID,	IL,	IS,	JP,	KΕ,	KG	, KP	KR,	ΚŻ,	LC,	LK,	LR,	LS,
		LT,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO	, NZ	PL,	RO,	RU,	SD,	SG,	SI,
	•	SK,	SL,	ТJ,	TM,	TR,	TT,	UA,	ŪĠ,	US	, UZ	, VN,	ΥU,	ZW			
	RW:	GH,	GM,	ΚE,	LS,	MW,	SD,	SZ,	ŪĠ,	ZW	, BF	BJ,	CF,	CG,	CI,	CM,	GA,
•		GN,	ML,	MR,	NE,	SN,	TD,	TG									
	2287															9980	428
AU	9872	613			Α		1998	1124		AU	1998	-7261	3		1	9980	428
BR	9809 2000	439			Α		2000	0613		BR	1998	-9439			1	9980	428
HU	2000	0318	7		A2		2001	0528		HU	2000	-3187			1	9980	428
JР	2001	5223	72		T		2001	1113		JP	1998	-5472	77		1	9980	428
US	6090	949			Α		2000	0718		US	1998	-6949	7		1	9980	429
EP	8755	10			A1		1998	1104		EP	1998	-3033	74		1	9980	430
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT,	LI,	LU,	NL,	SE,	MC,	PT,
		ΙE,	SI,	LT,	LV,	FI,	RO								•		
MX	9909	883			Α		2000	0331		MX	1999	-9883			1	9991	027
PRIORIT	PRIORITY APPLN. INFO.:									US	1997	-4517	7P		P 1	9970	430
										WO	1998	-US85	09	,	W 1	9980	428
OTHER SO	OTHER SOURCE(S):						T 13	0:37	69;	MAR	PAT :	130:3	769				

## \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The title compds. [I; Y = Cl, Br, I, SO2(C1-4 alkyl), etc.] were prepd. by AB reacting benzo[b]thiophene II [R51, R52 = hydroxy protecting groups] with benzoyl chloride III [R8 = acyl activating group] in the presence of a boron trihalide such as BCl3. Compds. I were reacted further with an amine HNR6R7 [R6, R7 = C1-4 alkyl; NR6R7 = piperidino, pyrrolidino, morpholino, etc.] to produce benzothiophenes IV and their salts.

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 11 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN L6 ACCESSION NUMBER: 1998:721501 CAPLUS Full-text

4

DOCUMENT NUMBER:

130:3768

TITLE:

Demethylation process for preparing benzo[b]thiophenes

INVENTOR(S):

Hoard, David Warren; Luke, Wayne Douglas

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

Eur. Pat. Appl., 13 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATION NO.	DATE
EP 875511	A1 19981104	EP 1998-303345	19980429
R: AT, BE, CH,	DE, DK, ES, FR, GB,	GR, IT, LI, LU, NL,	SE, MC, PT,
IE, SI, LT,	LV, FI, RO		
CA 2236254	A1 19981030	CA 1998-2236254	19980427
JP 11005789	A 19990112	JP 1998-118628	19980428
US 5994547	A 19991130	US 1998-69500	19980429
PRIORITY APPLN. INFO.:	•	US 1997-45156P	19970430
OTHER SOURCE(S):	CASREACT 130:3768;	MARPAT 130:3768	
GT			

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

$$\begin{array}{c|c} & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ &$$

AB The prepn. of benzo[b]thiophenes I [R1, R2 = C1-4 alkyl; NR1R2 = piperidino, pyrrolidino, etc.] by the acylation of alkoxy protected starting materials followed by demethylation of II using essentially odorless thiol compound (2methyl-5-t-Bu-benzenethiol) are provided herewith. Demethylation may be carried out in the same reaction vessel without isolation of the acylated, protected material.

REFERENCE COUNT:

10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CAPLUS COPYRIGHT 2007 ACS on STN ANSWER 12 OF 34 L6 1998:721498 CAPLUS Full-text

ACCESSION NUMBER: DOCUMENT NUMBER:

TITLE:

Process for preparing benzoic acid derivative

intermediates and benzothiophene pharmaceuticals

INVENTOR (S): PATENT ASSIGNEE(S): SOURCE:

Chelius, Erik Christopher Eli Lilly and Company, USA Eur. Pat. Appl., 16 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

#### PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATION NO.	DATE
EP 875507	A1 19981104	EP 1998-303340	19980429
R: AT, BE, CH,	DE, DK, ES, FR, GB,	GR, IT, LI, LU, NL,	SE, MC, PT,
IE, SI, LT,	LV, FI, RO		
CA 2231013	A1 19981030	CA 1998-2231013	19980304
JP 10316674	A 19981202	JP 1998-116564	19980427
PRIORITY APPLN. INFO.:		US 1997-45162P	P 19970430
OTHER SOURCE(S):	CASREACT 130:3767;	MARPAT 130:3767	
GI	,		

The novel intermediates Y1(CH2)nNR1R2 [R1, R2 = C1-4 alkyl; NR1R2 = piperidino, pyrrolidino, morpholino, etc.; n = 2-3; Y1 = p-toluenesulfonyloxy, methylsulfonyloxy, trifluoromethylsulfonyloxy, 2,2,2-trifluoroethylsulfonyloxy, trifluoroacetoxy], useful as intermediates in synthesis of benzothiophenes I and their salts, were prepared by reaction a hydroxylamine HO(CH2)nNR1R2 with W2O and W(halo) [W = p-toluenesulfonyl, methylsulfonyl, trifluoromethylsulfonyl, etc.].

THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1998:719256 CAPLUS Full-text

19

DOCUMENT NUMBER: 130:3764

TITLE: A regioselective alkylation process for preparing

substituted benzo[b]thiophenes

INVENTOR(S): McGill, John McNeil, III; Miller, Randal Scot

PATENT ASSIGNEE(S): Eli Lilly and Co., USA SOURCE: PCT Int. Appl., 22 pp.

OURCE: PCT Int. Appl., 22 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

REFERENCE COUNT:

PATENT NO	PATENT NO.						i	APPL	ICAT:	ION 1	. 07		D	ATÉ	
				-	-,								-		
WO 9848792	2		A1		1998:	1105	1	WO 1	998-1	JS84'	77		1	9980	428
W: AI	L, AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CU,	CZ,	DE,
DI	C, EE,	ES,	FI,	GB,	GE,	GH,	GM,	GW,	HU,	ID,	IL,	IS,	JP,	ΚE,	KG,
KI	, KR,	ΚŻ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX,
NC	), NZ,	PL,	ΡŤ,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	TJ,	TM,	TR,	TT,
UA	A, UG,	US,	UZ,	VN,	YU,	ZW,	AM,	AZ,	BY,	KG,	ΚŻ,	MD,	RU,	ТJ,	TM
RW: GH	I, GM,	KE,	LS,	MW,	SD,	SZ,	UG,	ZW,	AT,	BE,	CH,	CY,	DE,	DK,	ES,

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG CA 1998-2287918 19980428 CA 2287918 **A1** 19981105 AU 9871653 Α 19981124 AU 1998-71653 19980428 EP 979075 20000216 EP 1998-918798 19980428 A1 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI JP 2001523252 T · 20011120 JP 1998-547259 19980428 20000215 US 1998-69276 19980429 US 6025495 Α US 1997-45132P 19970430 PRIORITY APPLN. INFO.: WO 1998-US8477 . 19980428 CASREACT 130:3764; MARPAT 130:3764 OTHER SOURCE(S):

$$0 \longrightarrow 0 \longrightarrow N \longrightarrow \mathbb{R}^{2}$$

AB The title benzo[b]thiophenes I [R1, R2 = C1-4 alkyl; NR1R2 = piperidino, pyrrolidino, morpholino, etc.; n = 2, 3] such as raloxifene, were prepared by the regioselective alkylation of benzothiophene II with Y(CH2)nNR1R2 [Y = C1, p-TsO] in the presence of a suitable base.

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1998:192131 CAPLUS Full-text

DOCUMENT NUMBER:

128:275070

TITLE:

GI

Benzothiophenes, formulations containing same, and

methods

INVENTOR(S):

Cullinan, George Joseph; Palkowitz, Alan David

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE:

U.S., 10 pp. CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

19980324 US 1997-787041 US 5731342 Δ

19970127 19970127

PRIORITY APPLN. INFO.: OTHER SOURCE(S):

US 1997-787041 MARPAT 128:275070

GI

Benzothiophene N-oxides [I; R1 = H, OH, alkoxy, OCO2(alkyl or aryl), OCO(alkyl AΒ or aryl), etc.; R2 = R1, Cl or F; R3 and R4 = alkyl or combine to form polymethylene or morpholine; X = CH2, CHOH, O or CO], useful for the treatment or prevention of medical indications associated with post-menopausal syndrome and breast cancer, are prepared Thus, [2-(4-hydroxyphenyl)-6hydroxybenzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone was oxidized using 30% aqueous H2O2 to give I [R1 = R2 = OH, R3R4 = (CH2)5, X = I reduce serum cholesterol compared to ovariectomized rats and do not cause a large increase in the number of eosinophils observed in the stromal layer of the ovariectomized rat uteri. In an osteoporosis test, I prevent bone loss in a general, dose-dependent manner. I were active in the MCF-7 proliferation assay and inhibited growth of DMBA-induced mammary tumors. A tablet formulation comprises: I 2.5-1000, cellulose 200-650, silicon dioxide 10-650, and stearic acid 5-15 mg/tablet.

I

REFERENCE COUNT:

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 15 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN L6

5

ACCESSION NUMBER:

1998:161136 CAPLUS Full-text

DOCUMENT NUMBER:

128:221639

TITLE:

Preparation of amorphous benzothiophenes for

pharmaceuticals

INVENTOR(S):

Cuff, George W.; Thakkar, Arvind L.

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA; Cuff, George W.; Thakkar,

Arvind L.

SOURCE:

PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PAT	PATENT NO.					D :	DATE		1	APPL	ICAT:	ION I	NO.		D	ATE	
	<b></b>					-									-		
WO	9808		<b>A1</b>		1998	0305	. 1	WO 1	997-1	US14	768		1:	99708	322		
	W:	AL,	AM,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	CA,	CN,	CU,	CZ,	EE,	GE,	GH,
	-	HU,	IL,	IS,	JP,	KE,	KG,	ΚP,	KR,	KZ,	LC,	LK,	LR,	LT,	LV,	MD,	MG,
		MK,	MN,	MW,	MX,	NO,	NZ,	PL,	RO,	RU,	SD,	SG,	SI,	SK,	SL,	ТJ,	TM,
		TR,	TT,	UA,	ŪĠ,	US,	UZ,	VN,	YU,	ZW							
	RW:	GH,	KE,	LS,	MW,	SD,	SZ,	UG,	ZW,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,

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ML, MR, NE, SN, TD, TG
                               19980304
                                          EP 1997-306426
                                                                 19970822
    EP 826682
                         A1
                         В1
                               20030312
    EP 826682
        R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO
    CA 2263175
                         A1
                               19980305
                                           CA 1997-2263175
                                                                 19970822
    AU 9742335
                         Α
                               19980319
                                           AU 1997-42335
                                                                 19970822
    AU 723987
                         В2
                               20000907
                                                                 19970822
    IN 182940
                         A1
                               19990814
                                           IN 1997-CA1549
                                                                 19970822
    BR 9713176
                         Α
                               20000208
                                          BR 1997-13176
    CN 1244124
                                           CN 1997-197434
                                                                 19970822
                               20000209
                         Α
                                           HU 2000-1172
                                                                 19970822
    HU 200001172
                         A2
                               20010628
    HU 200001172
                        A3
                               20020128
    NZ 333839
                         Α
                               20010629
                                          NZ 1997-333839
                                                                 19970822
    IL 128641
                       Α
                               20011031
                                           IL 1997-128641
                                                                 19970822
    TR 9900403
                        T2
                               20020121
                                          TR 1999-403
                                                                 19970822
                                           JP 1998-511744
                         Т
                               20020514
                                                                 19970822
    JP 2002514174
                                          AT 1997-306426
    AT 234295
                         Т
                               20030315
                                                                 19970822
                                           ES 1997-306426
    ES 2195089
                         Т3
                               20031201
                                                                 19970822
                                                                 19970825
                               19990225
                                           ZA 1997-7617
    ZA 9707617
                         Α
                                          US 1997-918741
                                                                 19970825
    US 6713494
                         B1
                               20040330
                               19990225
                                          NO 1999-914
    NO 9900914
                         Α
                                                                 19990225
                                           KR 1999-701682
                                                                . 19990227
    KR 2000035941
                       Α
                               20000626
                                                              P 19960828
PRIORITY APPLN. INFO.:
                                           US 1996-24831P
                                           WO 1997-US14768
                                                              W 19970822
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OTHER SOURCE(S): MARPAT 128:221639

AB A method for prepg. an amorphous form of a benzothiophene such as raloxifene is described. Thus, raloxifene-HCl was prepared by a series of reactions starting from 3-methoxybenzenethiol and 4'-methoxyphenacyl bromide. A formulation contained PEG-1450 70, spray-dried lactose 1.5, colloidal SiO2 1.5, Polysorbate-80 2.0, and raloxifene-HCl 25%. The bioavailability of raloxifene-HCl and the pharmacol. effects of this compound on osteoporosis and hyperlipidemia were determined

REFERENCE COUNT:

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1997:640660 CAPLUS Full-text

1

DOCUMENT NUMBER:

127:307297

TITLE:

Preparation of 3-[4-(2-aminoethoxy)benzoyl]-2-aryl-6-

hydroxybenzo[b]thiophenes.

INVENTOR (S):

Jones, Charles David; McGill, John McNeill, III

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA; Jones, Charles David; McGill,

John McNeill, III

SOURCE:

PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

1

FAMILY ACC. NUM. COUNT:

AMILII ACC. NOM. COOMI.

PATENT INFORMATION:

PAT	PATENT NO.					<b>D</b> :	DATE		;	APPL	ICAT:	ION 1	NO.		D	ATE	
						-									-		
WO	9734	888			<b>A</b> 1		1997	0925	1	WO 1	996-1	US39:	34		1.	9960:	320
	W:	AL,	AM,	AT,	AU,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CZ,	DE,	DK,	EE,	ES,
		FI,	GB,	GE,	HU,	IS,	JP,	KE,	KG,	ΚP,	KR,	KZ,	LK,	LR,	LS,	LT,	LU,
		LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,
		SI,	SK,	ТJ,	TM,	TR,	TT,	UA,	UG,	US,	UZ,	VN,	AM,	ΑZ,	BY,	KG,	ΚZ,
		MD,	RU,	TJ,	TM												
	RW:	ΚE,	LS,	MW,	SD,	SZ,	UG,	AT,	BE,	CH,	DE,	DK,	ES,	FI,	FR,	GB,	GR,

IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG CA 2249406 **A1** 19970925 CA 1996-2249406 19960320 AU 9652586 Α 19971010 AU 1996-52586 19960320 EP 888331 19990107 EP 1996-908892 19960320 A1 AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI JP 2000506885 Т 20000606 JP 1997-533424 19960320 19980821 US 6008377 Α 19991228 US 1998-125848 PRIORITY APPLN. INFO.: US 1996-13674P 19960319 WO 1996-US3934 19960320 W

OTHER SOURCE(S):

CASREACT 127:307297; MARPAT 127:307297

GI

Title compds. (I; R1 = H, OH; R2, R3 = alkyl; R2R3N = pyrrolidino, piperidino, hexamethyleneimino, morpholino; HX = HCl, HBr) were prepared by reaction of PhOCH2CH2NR2R3.HX (variables as above) with acyl derivative (II; R4 = H, alkoxy; R5 = alkyl; R6 = Cl, Br, OH) in the presence of BX3. Thus, 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene-3-carbonyl chloride (preparation given), and Ph 2-N-piperidinylethyl ether hydrochloride (preparation given) in 1,2-dichloroethane at 0° were treated with BCl3 in 1,2-dichloroethane at 0° followed by warming to 35° for 16-20 h to give 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride 1,2-dichloroethane solvate.

II

L6 ANSWER 17 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1997:124441 CAPLUS Full-text

DOCUMENT NUMBER:

126:143973

TITLE:

Diaryl vinyl sulfoxides, a process for their synthesis, and their use in the preparation of

benzothiophene derivatives

INVENTOR(S):

Aikins, James A.; Miller, Randal S.; Zhang, Tony Y. Eli Lilly and Co., USA; Aikins, James A.; Miller,

Randal S.; Zhang, Tony Y.

SOURCE:

PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT ASSIGNEE(S):

PATENT NO.

KIND DATE

APPLICATION NO.

DATE

						-			-		- <b></b>				-		
WO	96406	591	•		A1		1996	1219	W	0 1	1996-	US91	63	•	1	9960	604
	W:	AL,	AM,	AT,	AU,	AZ;	BB,	BG,	BR, I	BY,	, CA,	CH,	CN,	CZ,	DE,	ĎK,	EE,
		ES,	FΙ,	GB,	GE,	HU,	IL,	IS,	JP,	KE,	, KG,	KP,	KR,	ΚZ,	LK,	LR,	LS,
•		LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW, I	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,
		SE,	SG													•	
	RW:	ΚE,	LS,	MW,	SD,	SZ,	ŪĠ,	AT,	BE, G	CH,	, DE,	DK,	ES,	FI,	FR,	GB,	GR,
		IE,							BF, I								
US	56590	87			Α		1997	0819	U	S 1	1995-	4787	06		1	.9950	607
US	63729	945			B1		2002	0416	U	S 1	1995-	4831	30		1	9950	607
CA	2220	145			<b>A</b> 1		1996	1219	C	A 1	1996-	2220	145		1	.9960	604
AU	96609	920			Α		1996	1230	A	U 1	1996-	6092	0		1	.9960	604
AU	69735	52			B2	•	1998	1001									
EP	83036	51			A1		1998	0325	E	P 1	1996-	9182	11 .	•	1	.9960	604
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	, IT,	LI,	LU,	NL,	SE,	PT,	ΙE,
		SI,	LT,	LV,	FI												
CN	11927	741			Α		1998	0909	Cl								
BR	96085	579			Α		1999	0105			1996-						
JP	11507	7061			T		1999				1996-						
	99009								H	U 1	1999-	922			1	.9960	604
	99009				Α3		2000										
	33703				Α		2000				1996-						
	33703						2001				1996-						
	10655				<b>A</b> 1		2004		_	_	1998-						
	97055						1997				1997-						
	5987				Α		1997	1203	N	0 2	2000-	5987	_		. 2		
									CI							0001	
PRIORITY	APPI	LN.	INFO	. :							L995-						
									_		1995-						
											L996-						
											1996-				<i>N</i> ]	.9960	604
OTHER SO	URCE	(S):			CASI	REAC	T 12	6:143	3973;	MΖ	ARPAT	126	:1439	973			

GI

AΒ

The invention is directed to new diarylvinyl sulfoxides I [R1, R2 = H, alkoxy, arylalkoxy, halo, amino; R3 = thermally labile or acid-labile alkyl, alkenyl,

or arylalkyl group], and to a new process for their synthesis. I are useful precursors for 2-aryl-substituted benzothiophenes II, which are in turn intermediates for the drugs III.HX [R1, R2 = H, halo, amino, OH; R4, R5 = alkyl; or NR4R5 = pyrrolidino, piperidino, hexamethyleneimino, morpholino; X = Cl, Br]. For instance, treatment of 4-MeOC6H4CH2COC6H4OMe-4 with TiCl4 in THF and reaction with Me3CSH and Et3N gave the vinyl sulfide (E)-4-MeOC6H4CH:C(SCMe3)C6H4OMe-4 [(E)-IV]. Alternatively, lithiation of 4-MeOC6H4CH2SCMe3 with BuLi and condensation with 4-MeOC6H4CHO gave (Z)-IV. Oxidation of either isomer of IV with a dilute AcOH solution of peracetic acid, in PhMe at -20°, gave the corresponding sulfoxide I [R1 = R2 = OMe; R3 = CMe3]. Dehydrative cyclization of, e.g., the (E)-sulfoxide, using p-MeC6H4SO3H catalyst under Dean-Stark conditions in PhMe, gave the benzothiophene II [R1 = R2 = OMe]. This was acylated by 4-(2piperidinoethoxy) benzoyl chloride HCl in the presence of BCl3 with concomitant demethylation to give the objective compound III.HCl [R1 = R2 = OH, NR4R5 = piperidino].

L6 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1997:113406 CAPLUS Full-text

DOCUMENT NUMBER:

126:117861

TITLE:

Process for the synthesis of benzo(b)thiophenes

INVENTOR(S): Aikins, James A.; Zhang, Tony Y.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA; Aikins, James A.; Zhang, Tony

ADDITION TO NO

שתיתרת

Υ.

SOURCE:

PCT Int. Appl., 35 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

DAMENIO NO

PAT	CENT	NO.							APPLICATION NO.						D	ATE	
WO	9640	676								WO :	 1996-1	 US91	- <i></i> 67		1	9960	604
	W:	AL,	AM,	ΑT,	AU,	AZ,	BB,	BG,	BR,	BY	, CA,	CH,	CN,	CZ,	DE,	DK,	EE,
		ES,	FI,	GB,	GE,	HU,	IL,	IS,	JP,	KE	, KG,	ΚP,	KR,	KZ,	LK,	LR,	LS,
		LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX	, NO,	ΝZ,	PL,	PT,	RO,	RU,	SD,
		SE,	SG														
	RW:	KΕ,	LS,	MW,	SD,	SZ,	ŪĠ,	ΑT,	ВĒ,	CH	, DE,	DK,	ES,	FI,	FR,	GB,	GR,
		ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ	, CF,	CG,	CI,	CM,	GA		
US	5606	076									1995-					9950	
CA	2223	096			A1		1996	1219		CA	1996-	2223	096		1	9960	604
AU	9660	921			Α		1996	1230		AU	1996-	6092	1		1	9960	604
ΑU	7029	28					1999										
EP	8597	70			. A1		1998	0826		EP	1996-	9182	12 .		1	9960	604
EP	8597				B1		1999										
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT,	LI,	LU,	NL,	SE,	PT,	ΙE,
		SI,	LT,	LV,	FI												
CN	1192	211					1998			CN	1996-	1959	43		1	9960	604
CN	1086	699					2002										
BR	9609	062					1999				1996-					9960	
	1150				_		1999				1997-					9960	
	9900						1999			HU :	1999-	912	•		1	9960	604
	9900						2000						•				
	2197						2001								_		
	1874						1999				1996-					9960	
	2140						2000				1996- 1996-					9960	
	8597				_		2000				1996-					9960	
ιr	1314	40			A		2000	1031		TL	1996-	1314	4 U		Τ.	9960	604

IL 122378	A	20010319	ΙL	1996-122378		19960604
NO 9705582	Α	19971203	NO	1997-5582		19971203
GR 3032666	<b>T</b> 3	20000630	GR	2000-400364		20000214
PRIORITY APPLN. INFO.:			US	1995-484536	Α	19950607
			$_{ ext{IL}}$	1996-122378	А3	19960604
			WO	1996-US9167	W	19960604

OTHER SOURCE(S): CASREACT 126:117861; MARPAT 126:117861

AB The present invention is directed to a process for the synthesis of 2-arylbenzo[b]thiophenes. E.g., 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene was prepared from desoxyanisoin and 2-methyl-2-propanethiol via tert-Bu 4,4'-dimethoxystilbenyl sulfoxide.

L6 ANSWER 19 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:649600 CAPLUS Full-text

DOCUMENT NUMBER:

125:266032

TITLE:

Phosphorous-containing benzothiophenes, their

preparation, their use in treating postmenopausal syndrome-associated indications and estrogen-dependent

diseases, and pharmaceuticals containing them

INVENTOR(S):

Bryant, Henry U.; Dodge, Jeffrey A.; Nissen, Jeffrey

s.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 19 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE			
EP 729964	A1	19960904	EP 1996-300878	19960209			
EP 729964	B1	20010509					
R: AT, BE, CH,	DE, DK	, ES, FR, C	BB, GR, IE, IT, LI, LU,	NL, PT, SE			
US 6479517	B1	20021112	US 1995-395944	19950228			
ES 2158242	<b>T</b> 3	20010901	ES 1996-300878	19960209			
CA 2169414	A1	19960829	CA 1996-2169414	19960213			
JP 08259560	Α	19961008	JP 1996-25281	19960213			
US 5998443	A	19991207	US 1997-946842	19971008			
PRIORITY APPLN. INFO.:			US 1995-395944	A 19950228			
OTHER SOURCE(S):	MARPAT	125:266032	2				
CT		,					

GI

Phosphorus-contg. benzothiophene compds. I [R1, R2 = H, OH, halo, OPO(0-alkyl)2, OPO(0-aryl)2, OPO(alkyl)2, OPO(aryl)2, OPO3-2, in which not more than one of R1 and R2 may be H, OH or halo; R3, R4 = CO(CH2)3, CO(CH2)4, alkyl, or R3 and R4 combine to form, with the nitrogen to which they are attached, piperidine, morpholine, pyrrolidine, 3-methylpyrrolidine, 3,3-dimethylpyrrolidine, 3,4-dimethylpyrrolidine, azepine, or pipecoline], and pharmaceutically acceptable salts thereof, are provided which are useful for the treatment of the various medical indications associated with postmenopausal syndrome, as well as estrogen-dependent diseases, including cancer of the breast, uterus and cervix. Also provided are intermediate compds. and processes useful for preparing the pharmaceutically active compds. of the invention, as well as pharmaceutical compns. containing compds. of the invention.

L6 ANSWER 20 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1996:319150 CAPLUS <u>Full-text</u>

DOCUMENT NUMBER:

125:86484

TITLE:

Preparation of vinyl sulfenic acid derivatives as

benzo[b]thiophene intermediates Hoard, David W.; Luke, Wayne D.

INVENTOR(S):

nouta, bavia w., bake, was

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 15 pp. CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.								APPLICATION NO.											
						19960430 US 1995-48269 19961219 CA 1996-22242													
	CA	2224	225	•		<b>A1</b>		1996		CA 1996-2224225						19960604			
	WO	9640	693			A1						19	96-1		1	19960604			
		W:	AL,	AM,	AT,	AU,	AΖ	, вв,	BG,	BR,	ВУ	ζ,	CA,	CH,	CN,	CZ,	DE,	DK,	EE,
			ES,	FI,	GB,	GE,	HU	, IL,	ıs,	JP,	KE	Ξ,	KG,	KP,	KR,	KZ,	LK,	LR,	LS,
								, MK,											
			SE,	SG	-	-	-		-			-							
		RW:	KE,	LS,	MW,	SD,	SZ	UG,	ΑT,	BE,	CH	ł,	DE,	DK,	ES,	FI,	FR,	GB,	GR,
								PT,											
	AU 9661003 A					1996	1230		ΑU	19	19960604								
		6980																	•
	EP 830362			A1	A1 19980325			EP 1996-918314						19960604					
		R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	۲,	IT,	LI,	LU,	NL,	SE,	PT,	ΙE,
			SI,	LT,	LV,	FI													
		1192									CN	19	96-	1959	47		1	9960	604
	CN	1068	883		•	В		2001	0725										
	BR	9608	847			Α		1999	0608		BR	19	96-	8847			• 1	9960	604
	JP	1150	7346			${f T}$		1999										9960	604
	HU	9900	923			A2		1999	0728		HU	19	99-	923			1	9960	604
	ΗU	9900	923			<b>A3</b>		2000											
		1221				Α		2001	0520		$_{ m IL}$	19	96-3	1221	27		1	9960	604
	ИО	9705	633			Α		1998	0128		NO	19	97-!	5633			1	9971	204
	CN	1330	071			Α		2002	0109		CN	20	00-3	1307	96		2	0001	212
PRIOR	TIS	APP	LN.	INFO	.:										92				
						•					US	19	95-4	4836	07		A 1	9950	607
											WO	19	96-1	JS94	60	,	W 1	9960	604

OTHER SOURCE(S): CASREACT 125:86484; MARPAT 125:86484

AB 4-R1C6H4CH:C(R9)C6H4R2-4 [I; R1,R2 = H, (ar)alkoxy, halo, NH2; R9 = SR4; R4 = OSi(R)3, NR5R6, SR8; R = (ar)alkyl, aryl; R5,R6 = H, (ar)alkyl; NR5R6 =

pyrrolidino, piperidino, etc.; R8 = (ar)alkyl, aryl] were prepared by treating I [R9 = SOR3; R3 = labile alk(en)yl or aryl] with a silylating agent optionally followed by reaction with HNR5R6 or HSR8. Thus, (E)-I (R1 = R2 = OMe)(II; R9 = SOCMe3)(preparation given) was treated with (Me2CSiNH)2CO in PhMe followed by Me2NH, in the same pot, to give I (R1 = R2 = OMe, R9 = SNMe2) as a mixture of (E) - and (Z) -isomers. The latter mixt was treated with TsOH to give 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophe ne.

ANSWER 21 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

1996:307324 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER: 124:343103

Preparation of unsolvated crystalline TITLE:

> 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy) benzoyl] benzo[b] thiophene

hydrochloride.

Smith Labell, Elizabeth; Luke, Wayne Douglas; McNeill INVENTOR(S):

McGill, John, III; Miller, Randal Scot

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: Ger. Offen., 18 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent LANGUAGE: German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19534744	A1	19960321	DE 1995-19534744	
US 5629425	Α	19970513	US 1994-308325	19940919
IN 1995CA00614	A	20050304	IN 1995-CA614	19950530
IN 1995CA00615	A	20050304	IN 1995-CA615	19950530
TW 389760	В	20000511	TW 1995-84105614	19950605
TW 412534	В	20001121	TW 1995-84105613	19950605
US 5731327	A	19980324	US 1995-467485	19950606
EG 21479	A	20011128	EG 1995-455	19950606
US 6399778	В1	20020604	US 1995-469093	19950606
US 6472531	B1	20021029	US 1995-469961	19950606
ES 2109882	A1	19980116	ES 1995-1774	19950913
ES 2109882	B1	19980816		
ES 2129293	A1	19990601	ES 1995-1775	19950913
ES 2129293	B1	20000116		
NL 1001194	A1	19960319	NL 1995-1001194	19950914
NL 1001194	C2	19970404		
NL 1001196	A1	19960319	NL 1995-1001196	19950914
NL 1001196	C2	19970404		
ZA 9507752	A	19970314	ZA 1995-7752	19950914
ZA 9507753	A	19970314	ZA 1995-7753	19950914
IL 115315	Α	19990922	IL 1995-115315	19950914
IL 115314	A	20000229	IL 1995-115314	19950914
IL 125283	Α	20010614	IL 1995-125283	19950914
IN 1995CA01111	Α	20051021	IN 1995-CA1111	19950914
CA 2158399	A1	19960320	CA 1995-2158399	19950915
CA 2158399	C	20010320		
CA 2158400	A1	19960320	CA 1995-2158400	19950915
CA 2158400	С	20061024		•
DK 9501027	A	19960320	DK 1995-1027	19950915
DK 175903	B1	20050606		
DK 9501028	Α	19960320	DK 1995-1028	19950915
DK 175897	B1	20050530		

NO	9503657			A		1996	0320	N	) :	1995-	3657			1	9950	915
	308107			B1		2000										
	9503658			Α		1996		N	) :	1995-	3658			1	9950	915
	313996			B1		2003										
	9503213			Α		1996		Sì	Ξ :	1995-	3213	•		1	9950	915
	520721			C2		2003								٠		
	9503214			Α			0320	SI	Ξ :	1995-	3214			1	9950	915
	509265			C2		1998										
	115259			B1			1230			1995-					9950	
	115260			B1			1230			1995-					9950	
	290343			-B6		2002				1995-					9950	
	292007			В6			0716			1995-					9950	
	9504402			A		1996		F.	Ι:	1995-	4402			1	9950	918
	112226			B1		2003								_		
	9504403			Α		1996				1995-		_			9950	
	2724655			A1		1996		FI	₹ :	1995-	1092	1		1	9950	918
	2724655			B1		1997						_		_		
	2293382			Α		1996			3 :	1995-	1902	8		1.	9950	918
	2293382			В			0819		_			_		_		
	2293602			A		1996		GI	3 :	1995-	1903	2		1.	9950	918
	2293602			В		1998						_		_		
	9531730			A		1996		Αl	J :	1995-	3173	0		1	9950	918
	691955			B2		1998						_		_		
	9531731			Α		1996		ΙA	J:	1995-	3173	1		1.	9950	918
	692907			B2		1998								_		
	08176147			A			0709	J		1995-	2382	11		1.	9950	918
	2860071			B2		1999		-						_		
	1127253			A		1996		CI	Ν.	1995-	1186	29		1	9950	918
	1075069			В			1121							_		
	08193081			A		1996				1995-		09			9950	
	11177			В		1996				1995-					9950	
	11178			В		1996				1995-					9950	
	9504059			A		1996				1995-					9950 9950	
	9504060			A		1996				1995 - 1995 -					9950 9950	
	2732020			A1		1996		. Pi	≺ .	1995-	1092	2		1	9950	310
	2732020			B1		1997		C)	т.	1995-	1104	4.0		7	9950	010
	1132205			A B		1996 2001		CI	ν.	1333-	1104	49		1	<b>7</b> 750	210
	1068324			A2		2001 1996		ш	7 -	1995-	2722			1	9950	010
	74178 75033						0328			1995-i					9950 9950	
	225417			A2 B1			1128		٠.	1995-	2/21			1	9930	910
	1009625			A3			0603			1995-	760			1	9950	918
	1009626			A3			0603			1995-					9950	
	2104278			C1			0210			1995-					9950	
	2104278			C1			0410			1995-					9950	
	9501542			A			1215			1995-					9950	
	691125	•		A5			0430			1995-:					9950	
	691431			A5			0731			2000-					9950	
	691478			A5			0731			1995-					9950	
	691594			A5			0831			1995 -					9950	
				B1			0131			1995-					9950	
	950483			B1			0228			1995-					9950	
	187686			B1			0930			1995-				,	9950	
	950482			B1			0430			1995-					9950	
	502957			A1		2007	0615	A.		L995-					9950	
	9609045			A1		1996	0328	WC		1995-1					9950	
		AT,	AU,					CA, C						EE,	ES,	FI,
	GB,	GE,	HU,	IS,	JP,	KE,	KG,	KP, F	CR,	KZ,	LK,	LR,	LT,	LU,	LV,	MD,
	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL, I	РΤ,	RO,	RU,	SD,	SE,	SG,	SI,	SK,
	.TJ,	TM														

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RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT,
             LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,
                                             DE 1995-19534745
     DE 19534745
                          A1
                                19960404
                                                                    19950919
                          B4
                                20040609
     DE 19534745
                                19960409
                                             AU 1995-37186
                                                                    19950919
     AU 9537186
                          Α
                                             EE 1997-55
                                                                    19950919
                          B1
                                20010416
     EE 3386
                                             SK 1997-233
                                                                    19950919
     SK 283502
                          В6
                                20030805
                                            DE 1995-19549755
     DE 19549755
                          B4
                                20050504
                                                                    19950919
                                19970109
                                             DK 1997-27
                                                                    19970109
     DK 9700027
                          Α
     DK 175887
                          В1
                                20050523
                                19970109
                                            DK 1997-28
                                                                    19970109
     DK 9700028
                          Α
                          В1
                                20050523
     DK 175886
                                                                    20011002
     CZ 290344
                          В6
                                20020717
                                             CZ 2001-3548
                                             US 2002-83179
                                                                    20020226
     US 2002173645
                          A1.
                                20021121
                                             US 1994-308325
                                                                 A 19940919
PRIORITY APPLN. INFO.:
                                                                 A 19950426
                                             US 1995-427914
                                             US 1995-469093
                                                                 A1 19950606
                                             IL 1995-115315
                                                                 A3 19950914
                                             CZ 1995-2402
                                                                 A3 19950915
                                             DE 1995-19534744
                                                                 A1 19950919
                                             WO 1995-US11872
                                                                 W 19950919
```

Title compd. (I) (raloxifene hydrochloride) having a specified X-ray AB diffraction pattern, was prepared Thus, 6-methoxy-2-(4methoxyphenyl)benzo[b]thiophene (preparation given) and 4-(2piperidinoethoxy) benzoyl chloride hydrochloride (preparation given) in CH2Cl2 was treated with BCl3 at 0 for 8 h and at 35° for 16 h to give I.1,2dichloroethane of 86.8% purity. The latter in MeOH was treated with NaOH and activated C followed by filtration, treatment with HCl, and crystallization to give 99.1% pure I.

ANSWER 22 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN 1996:256453 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER:

124:289251

TITLE:

Process for preparing benzoic acid derivative

intermediates and benzothiophene pharmaceutical agents

INVENTOR(S):

Kjell, Douglas Patton; Perry, Fred Mason

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

Eur. Pat. Appl., 18 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

1

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA.	TENT NO.		KIND	DATE	APPLICATION NO.	DATE
ΕP	699672	4	A1	19960306	EP 1995-306050	19950830
ΕP	699672		B1	19980422		
	R: AT, 1	BE, CH,	DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU,	NL, PT, SE
US	5631369		A	19970520	US 1994-298636	19940831
IL	128881		A	20001206	IL 1995-128881	19950828
CA	2157236		A1	19960301	CA 1995-2157236	19950830
FI	9504067		Α	19960301	FI 1995-4067	19950830
HU	73141		A2	19960628	HU 1995-2537	19950830
ΗŲ	222121		В1	20030428		
BR	9503846		Α	19960917	BR 1995-3846	19950830
AΤ	165355		T	19980515	AT 1995-306050	19950830
ES	2114721		<b>T</b> 3	19980601	ES 1995-306050	19950830

TW 427975	В	20010401	TW	1995-84109069		19950830
JP 08119964	Α	19960514	JP	1995-223183		19950831
US 5750688	Α	19980512	US	1996-629862		19960409
PRIORITY APPLN. INFO.:			US	1994-298636	Α	19940831
			IL	1995-115092	A3	19950828

OTHER SOURCE(S):

MARPAT 124:289251

GI

$$C(CH_2) \text{ nNR}^{1}R^2$$
 $C(CH_2) \text{ nNR}^{1}R^2$ 
 AB The present invention provides a novel process for prepg. novel compds. of formula HO2C(p-C6H4)O(CH2)nNR1R2 [R1, R2 = C1-C4 alkyl, combine to form piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; n = 2, 3] or a pharmaceutically acceptable salt thereof, comprising (a) reacting a haloalkyl amine of formula X(CH2) nNR1R2 [X = halo; R1, R2, and n are as defined above], with a compds. of formula RO2C(p-C6H4)OH [R = C1-C6 alkyl], in the presence of an alkyl acetate solvent and a base; (b) extracting the reaction product of step (a) with an aqueous acid; and (c) cleaving the ester of the reaction product from step (b) to form an acid. The present invention further provides a novel process for preparing compds. of Formula I [R1, R2 = C1-C4 alkyl, or combine to form piperidinyl, pyrrolidino, methylpyrrolidino, dimethylpyrrolidinyl, morpholino, dimethylamino, diethylamino, or 1hexamethyleneimino; R3, R4 = H, hydroxy protecting group; n = 2, 3] or a pharmaceutically acceptable salt thereof, comprising (a) reacting a haloalkyl amine of formula X(CH2)nNR1R2 [X = halo; R1, R2, and n are as defined above], with a compound of formula RO2C(p-C6H4)OH [R = C1-C6 alky], in the presence of an alkyl acetate solvent and a base; (b) extracting the reaction product from step (a) with an aqueous acid; (c) cleaving the ester of the reaction product from step (b) to form an acid; (d) reacting the extracted product from step (c) with a compound of formula II [R3 and R4 are as defined above], or a pharmaceutically acceptable salt thereof; (e) optionally removing R3 and R4 hydroxy protecting groups of the reaction product from step (d); and (f) optionally forming a salt of the reaction from either steps (d) or step (e).

L6 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 19

1996:150242 CAPLUS Full-text

DOCUMENT NUMBER:

124:202950

TITLE:

Preparation of benzothiophene glucopyranosides as

antihyperlipidemics.

INVENTOR(S):

Dodge, Jeffrey Alan; Frolik, Charles Alan; Lindstrom,

Terry Donald; Lugar, Charles Willis Iii; Staten,

Gilbert Stanley

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 20 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	TENT NO.	•	KINI	DATE		PLICATION NO.		DATE
·								
	683170				EP	1995-303265		19950516
•	R: AT,	BE, CH,	DE,			R, IE, IT, LI,		
US	5567820		Α			1995-404701		
US	6723739			20040420		1995-405555		
CA	2149501		<b>A1</b>	19951121	CA	1995-2149501		19950516
	9503975		Α	19961118	ZA	1995-3975		19950516
AT	184880 2136799		${f T}$	19991015	AT	1995-303265		19950516
ES	2136799	•	Т3	19991201	ES	1995-303265		19950516
AU	9520121		Α	19951130	AU	1995-20121		19950517
AU	683734		B2	19971120				
JР	07316180		Α	19951205	JP	1995-118338		19950517
FI	9502420		Α	19951121	FI	1995-2420		19950518
NO	9501954		Α	19951121	NO	1995-1954		19950518
NO	304686		B1	19990201				
CN	1116626		Α	19960214	CN	1995-106322		19950518
CN	1039013		В	19980708				
BR	9502079	•	Α	19960305	BR	1995-2079		19950518
HU	73788		A2	19960930	HU	1995-1466		19950518
HU	219335		В	20010328				
IL	113780		Α	19990620	$_{ m IL}$	1995-113780		19950518
GR	3032142		Т3	20000427	GR	1999-403228		19991215
US	20041670	80		20040826	US	2004-778865		20040212
PRIORIT	Y APPLN.	INFO.:			US	1994-246655	P	19940520
		,			US	1995-405555	P	1 19950315
				•				

OTHER SOURCE(S):

CASREACT 124:202950

ОН

ΙI

Raloxifene metabolites (I) and (II) and their hydrochloride salts were AB prepared Thus, I and II, prepared from 6-tert-butyldimethylsilylraloxifene and 4'-tert-butyldimethylsilylraloxifene and Me 1,2,3,4-O-tetraacetyl-Dglucopyranuronate, at 1.3 mg/kg in rats decreased serum cholesterol by 44.5% and 56.8%, resp. Drug formulations are given.

ANSWER 24 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN L6

1996:123714 CAPLUS Full-text ACCESSION NUMBER:

DOCUMENT NUMBER: 124:155994

Pharmaceutical compositions containing TITLE:

2-phenyl-3-aryoylbenzothiophenes for for inhibiting

bone loss and lowering serum cholesterol

Draper, Michael W. INVENTOR(S):

Eli Lilly and Co., USA PATENT ASSIGNEE(S): Can. Pat. Appl., 31 pp. SOURCE:

CODEN: CPXXEB

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	CA 2141999			CA 1995-2141999	
	US 5478847		19951226		
	ZA 9500976	Α	19960807		
	NZ 314699	Α	20000728	NZ 1995-314699	19950207
	EP 674903	A1	19951004	EP 1995-300842	19950210
	R: AT, BE, C	H, DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU	, NL, PT, SE
	NO 9500774	Α	19950904	NO 1995-774	19950228
	RU 2100024		19971227	RU 1995-102778	19950228
	RU 2150275	C1	20000610	RU 1996-119781	19950228
	AU 9513551	Α	19950907	AU 1995-13551	19950301
	AU 702575	B2	19990225		
	JP 07267861	. <b>A</b>	19951017	JP 1995-41769	19950301
	JP 2818384	B2 .	19981030		
	BR 9500784	Α	19951024	BR 1995-784	19950301
	CN 1119530	Α	19960403	CN 1995-100021	19950301
	HU 72638	A2	19960528	HU 1995-634	19950301
	JP 10291932	A	19981104	JP 1998-107550	19950301
	JP 10310525	A	19981124	JP 1998-107549	19950301
	US 5610168	A	19970311	US 1995-422289	19950414
	US 5641790	A	19970624	US 1995-422417	19950414
	US 5747510	Α	19980505	US 1997-788984	19970127
	US 39050	E1	20060328	US 2003-375274	. 20030227
PRIO	RITY APPLN. INFO.:			US 1994-205012	
				JP 1995-41769	A3 19950301
				US 1995-422417	
מג	A method of inhi	hiting bor	a loss or	resorption or lowering	

A method of inhibiting bone loss or resorption, or lowering serum cholesterol, AB comprises administering to a human in need thereof pharmaceutical compns. containing 2-phenyl-3-aryoylbenzothiophenes, salt or solvate thereof, in a low dosage amount Raloxifene (I) at 50-200 mg decreased LDL cholesterol in postmenopausal women and there was no changes in HDL cholesterol level. A capsule contained I 150, starch 150, starch flowable powder 397, and silicone fluid 350 3.0 mg.

ANSWER 25 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1995:991025 CAPLUS Full-text

DOCUMENT NUMBER:

124:106673

TITLE:

Methods for lowering serum cholesterol

INVENTOR (S):

Black, Larry J.; Bryant, Henry U.; Cullinan, George

J.; Kauffman, Raymond F.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 14 pp. Cont.-in-part of U.S. Ser. No. 995, 222,

abandoned.

CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.		DATE	APPLICATION NO.	
 US 5464845	Α	19951107	US 1993-159159	/ 19931130
TW 383306	В	20000301	TW 1993-82100751	19930204
RU 2123335	C1	19981220	RU 1993-55026	19931213
ZA 9309427	A	19950615	ZA 1993-9427	19931215
SK 279271	В6	19980805	SK 1993-1421	19931215
IL 108042	A	19980104	IL 1993-108042	19931216
CZ 283863	B6	19980617	CZ 1993-2790	19931216
HU 69686	A2	19950928	HU 1993-3676	19931220
HU 223342	B1	20040628	•	
RO 113806	B1	19981130	RO 1993-1739	19931220
PL 177349	B1	19991029	PL 1993-301579	19931220
CA 2112017	A1	19940623	CA 1993-2112017	19931221
CA 2112017	С	20050614	·	
NO 9304740	A	19940623	NO 1993-4740	19931221
AU 9352578	A	19940707	AU 1993-52578	19931221
AU 669235	B2	19960530		•
BR 9305182	A	19940816	BR 1993-5182	19931221
JP 06234632	Α	19940823	JP 1993-323825	19931222
JP 3197129	B2	20010813		
CN 1094042	Α	19941026	CN 1993-121277	19931222
CN 1043608	В	19990616		
AT 233559	T	20030315	AT 1993-310438	19931222
ES 2193142	Т3	20031101	ES 1993-310438	19931222
PRIORITY APPLN. INFO.:			US 1992-995222	B2 19921222
OTHER SOURCE(S):	MARPAT	124:106673		
GI			. •	•

AB A method of lowering serum cholesterol levels comprising administering to a patient a serum cholesterol lowering amount of a compound I wherein n is 0, 1 or 2; R is hydroxyl, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R1 is hydrogen, hydroxyl, chloro, bromo, methoxy, alkanoyloxy, cycloalkanoyloxy, substituted or unsubstituted aroyloxy, or substituted or unsubstituted aryloxycarbonyloxy; R2 is a heterocyclic ring (pyrrolidino, piperidino, or hexamethyleneimino); or a pharmaceutically acceptable salt or solvate thereof.

The tested compds. lowered LDL without significantly affecting primary sex targets.

L6 ANSWER 26 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1995:934099 CAPLUS Full-text

DOCUMENT NUMBER:

123:339764

TITLE:

Processes for preparing 3-(benzoy1)-2-(4-

hydroxyphenyl) benzothiophenes

INVENTOR(S):

Dodge, Jeffrey Alan; Stocksdale, Mark Gregory

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA Eur. Pat. Appl., 19 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE		
EP 675121	A1	19951004	EP 1995-302076	19950328		
R: AT, BE, CH,	DE, DK	, ES, FR,	GB, GR, IE, IT, LI, LU,	NL, PT, SE		
CA 2145614	A1	19951001	CA 1995-2145614	19950327		
JP 07278138	Α	19951024	JP 1995-73418	19950330		
US 5808061	Α	19980915	US 1995-503444	19950717		
PRIORITY APPLN. INFO.:			US 1994-220853	A 19940331		
OTHER SOURCE(S):	CASREA	CT · 123:339	9764; MARPAT 123:339764			
GI						

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\$$

The title compds. [I; R1R2 = C4-6 polymethylene, CH2CH(CH3)CH2CH2, CH2C(CH3)2CH2CH2, CH2CH2OCH2CH2] [e.g., [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methan one hydrochloride], useful for the treatment of osteoporosis in post-menopausal women (no data), are prepared by: (a) coupling a benzothiophene (II; X = H) with a (hydroxyethyl)amine HOCH2CH2N(R1)R2 in the presence of P(Ph3) and di-Et azodicarboxylate; or (b) reacting a benzothiophene (II; X = CH2CH2Z; Z = leaving group) with pyrrolidine, piperidine, hexamethyleneimine, methylpyrrolidine, dimethylpyrrolidine, or morpholine; (c) deprotecting the 6-and 4-position hydroxy groups of the reaction product of step (a) or step (b);

and (d) optionally salifying or forming a solvate of the reaction product of step (c).

ANSWER 27 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1995:661193 CAPLUS Full-text

DOCUMENT NUMBER:

123:111843

TITLE:

2-amino-3-aroylbenzo[b]thiophenes and methods for

preparing and using same to produce 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2aminoethoxy) benzoyl] benzo[b] thiophene

INVENTOR(S):

Godfrey, Alexander G. Eli Lilly and Co., USA

PATENT ASSIGNEE(S): SOURCE:

GI

U.S., 9 pp.

CODEN: USXXAM

DOCUMENT TYPE:

Patent .

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	TENT															ATE		
US	5420	349			Α		1995	0530	τ	JS 1	994-	25864	41		1	9940	510	
CA	2192	096			A1		1995	1221	(	CA 1	995-	2192	096		1	9950	507	
WO	9534	536			A1		1995	1221	V	<b>VO</b> 1	995-1	US73	9,9		1	9950	507	
	W:	AM,	AT,	AU,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CZ,	DΕ,	DK,	EE,	ES,	FI,	
		GB,	GE,	HU,	IS,	JP,	KE,	KG,	KP,	KR,	ΚZ,	LK,	LR,	LT,	LU,	LV,	MD,	
		MG,	MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	ΤJ,	
		TM,	TT															
	RW:	KE,	MW,	SD,	SZ,	ŪĠ,	ΑT,	ΒE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	ΙE,	IT,	
		LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	ML,	MR,	ΝE,	
		SN,	TD,	TG														
AU EP	9528	236			Α		1996	0105	7	\U 1	995-3	2823	6		1	9950	507	
EP	7641	50			<b>A1</b>		1997	0326	I	EP 1	995-	92380	04		1	9950	507	
	7641														·			
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	ΙE,	IT,	LI,	LU,	MC,	NL,	PT,	SE
HU.	7600	0			A2		1997	0630	I	TU 1	996-	3404			1:	9950	507	
HU	2138	34			В		1997	1028							•			
HU	2138 7652	5			A2		1997	0929	I	IU 1	996-	3403			1:	9950	507	
HU	2162	72			В		1999	0528								*		
BR	9507	968			Α		1997	1118	I	3R 1	995-	7968			1:	9950	507	
	1050																	
AT	1860	50			T		1999	1115	7	AT 1	995-	92380	04		1:	9950	507	
ES	2139	222			Т3			0201										
HU	2178	22			В		2000	0428	. I	łU 1	998-2	2648 <sup>.</sup>			1:	9950	507	
FI	9604	854																
GR	3032	409			Т3		2000	0531	(	3R 2	000-4	40010	06		2	0000	119	
PRIORIT											994-2							
									V	VO 1	995-1	JS739	9	1	<b>v</b> 1:	9506	507	
OTHER S	OURCE	(S):			CASI	REAC	T 12	3:11:	1843;	MA.	RPAT	123	:1118	343				

A group of 2-amino-3-aroyl-benzo[b]thiophenes (I) are prepd. by prepg. an  $\alpha$ -AB hydroxy thioacetamide 4-ROC6H4CH(OH)C(:S)NR9R9 (II) wherein R, R8 and R9 independently represent C1-C6 alkyl; comprising: (a) reacting an alkyl imidate of the formula 4-ROC6H4CH(OH)C(:NH.protic acid)OR''' where R''' is C1-C6 alkyl, with a sulfur compound to yield a thioester of the formula 4-ROC6H4CH(OH)C(:S)OR'''; (b) reacting the thioester with a dialkylamine of the formula HNR8R9 to yield the  $\alpha$ -hydroxy thioacetamide; said steps being conducted without isolation or purification of the thioester., cyclizing II, and subsequently acylating the benzo[b]thiophene to yield the 2-amino-3-aryl derivative These compds. may be treated with suitable Ph Grignard reagents, and 'after deprotection, yield 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thi ophene. %Thus, e.g., p-anisaldehyde was converted to p- methoxybenzaldehyde cyanohydrin (80% yield) and subsequently to the Me imidate 4-MeOC6H4CH(OH)C(:NH.HCl)OMe (85-90% yield); reaction of the latter with H2S/Me2NH afforded  $\alpha$ -(4-methoxy phenyl)- $\alpha$ -hydroxy- N,Ndimethylthioacetamide (70%) which was cyclized with methanesulfonic acid to 2-N, N-dimethylamino-6-methoxybenzo[b]thiophene (79%); acylation of the latter with 4-(2-piperidinoethoxy) benzoyl chloride hydrochloride (autocatalytic) afforded 2-N, N-dimethylamino-6-methoxy-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride (I; R = Me, R3 = R4 = Me, R'' = 2-piperidinoethyl; 74%) which underwent Grignard reaction with 4methoxyphenylmagnesium bromide to afford 2-(4-methoxyphenyl)-6- methoxy-3-[4-(piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride (90%); deprotection of the latter with AlCl3/propanethiol afforded 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thi ophene hydrochloride (95% yield).

ANSWER 28 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN. ACCESSION NUMBER:

DOCUMENT NUMBER:

1995:362913 CAPLUS Full-text

122:213884

TITLE:

A chemical probe for the estrogen receptor: synthesis

of the 3H-isotopomer of raloxifene

AUTHOR(S):

Dodge, Jeffrey A.; Stocksdale, Mark G.; Jones, C.

David

CORPORATE SOURCE:

Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE:

Journal of Labelled Compounds & Radiopharmaceuticals

(1995), 36(1), 43-9

CODEN: JLCRD4; ISSN: 0362-4803

PUBLISHER:

Wiley Journal

DOCUMENT TYPE: LANGUAGE:

English

Radiolabeled raloxifene (LY156758) was prepd. by tritium gas hydrogenolysis of AR a 3-aroyl bis-brominated precursor. The requisite halogenated intermediate was accessed by regioselective aroylation of 6-methoxy-2-(4methoxyphenyl)benzo[b]thiophene with 3,5-dibromo-4-[2-(1piperdinyl)ethoxy]benzoyl chloride. Selective deprotection of the aryl Me ethers in the presence of the ethoxy side-chain followed by palladium

catalyzed halogen-tritum exchange provided the target compound with a specific activity of 30.1 Ci/mmol.

L6 ANSWER 29 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1987:433189 CAPLUS Full-text

DOCUMENT NUMBER: 107:33189

TITLE: Treatment of mammary cancer

INVENTOR(S): Black, Larry J.; Clemens, James A.

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: U.S., 10 pp. Cont. of U.S. Ser. No. 289,360,

abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4656187 PRIORITY APPLN. INFO.:	A	19870407	US 1983-556875 US 1981-289360	19831201
AB A method of inhib	iting th	e arowth of	estrogen-dependent	mammary cancers
comprises adminis hydroxyphenyl)-3apprx.5 mg/kg/da combination compr weight of II. I pyrrolidinoethoxy 2-(4-methoxypheny α-bromo-4-methoxy given for 8 wks treceiving the com	tering a [4-(2-py y of a 2 ises ap hydrochl )benzoic 1)benzo[ acetophe o rats w bination had onl	bout 20 mg/rrolidinoet nd compound prx.4 parts oride was pacid with b]thiophene none). Orath induced treatment y a very mo	kg/day of a 1st comp hoxy)benzoyl]benzo[b tamoxifen (II). Al by weight of I and repared by reacting thionyl chloride and (prepared from 3-me l doses of I 20 and mammary tumors. Ha experienced a total dest growth of their	ound 6-hydroxy-2-(4- ]th iophene (I) and so, a pharmaceutical .apprx.1 part by 4-(2- then with 6-methoxy- thoxybenzenethiol and II 5 mg/kg/day were lf of the rats regression of their

L6 ANSWER 30 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1984:448784 CAPLUS Full-text

DOCUMENT NUMBER:

101:48784

TITLE:

Antiestrogens. 2. Structure-activity studies in a series of 3-aroyl-2-arylbenzo[b]thiophene derivatives leading to [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride (LY 156758), a remarkably effective estrogen antagonist with only minimal intrinsic

estrogenicity

AUTHOR(S): Jones, Charles D.; Jevnikar, Mary G.; Pike, Andrew J.;

Peters, Mary K.; Black, Larry J.; Thompson, Allen R.;

Falcone, Julie F.; Clemens, James A.

CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN,

46285, USA

SOURCE: Journal of Medicinal Chemistry (1984), 27(8), 1057-66

CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE:

Journal

LANGUAGE:

English

In an effort to prep. nonsteroidal antiestrogens demonstrating greater AB antagonism and less intrinsic estrogenicity than those currently available, a series of 3-aroyl-2-arylbenzo[b]thiophene derivs. was synthesized. These compds. were prepared by Friedel-Crafts aroylation of appropriate O-protected 2-arylbenzo[b]thiophene nuclei with basic side-chain-bearing benzoyl chlorides followed by removal of the protective groups to provide the desired compds. containing both hydroxyl and basic side-chain functionality. A particularly useful method for the cleavage of aryl methoxy ethers without removal of (dialkylamino) ethoxy side chain functionality elsewhere in the mol. was AlCl3/EtSH. The benzothiophene derivs. were tested for their ability to inhibit the growth-stimulating action of estradiol on the immature rat uterus. Seemingly minor changes in the side-chain amine moiety had profound effects on the ability of the compds. to antagonize estradiol. Analogs having basic side chains containing cyclic (pyrrolidine, piperidine, and hexamethyleneamine) moieties had less intrinsic estrogenicity and antagonized estradiol action more completely than their noncyclic counterparts. The most effective antiestrogen in the series, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1- piperidinyl)ethoxy]phenyl]methanone (I) [84449-90-1], elicited a modest uterotropic activity that did not increase with increasing dose. In antagonism of estradiol, I exhibited a degree of inhibition surpassing that of tamoxifen at any dose tested. The new benzothiophene antiestrogen also had high affinity for rat uterine cytoplasmic estrogen receptor and was an inhibitor of the growth of DMBA-induced rat mammary tumors.

L6 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1984:156501 CAPLUS Full-text

DOCUMENT NUMBER:

100:156501

TITLE:

Antiestrogenic and antiandrogenic benzothiophenes

INVENTOR(S):

Jones, Charles D.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 23 pp. Cont.-in-part of U.S. Ser. No. 246,335,

abandoned.
CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

T: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	API	PLICATION NO.	•	DATE
					-	
US 4418068	A	19831129	US	1981-331042		19811216
ZA 8202247	Α	19831130	ZA	1982-2247		19820401
PRIORITY APPLN. INFO.:			US	1981-246335	<b>A2</b>	19810403
OTHER SOURCE(S):	CASREA	ACT 100:1565	01			

AB Antiandrogenic and antiestrogenic [(piperidinoethoxy)benzoyl]benzothiophen es I [R,R1 = H, R2CO; R2 = H, cycloalkyl, (un)substituted alkyl, Ph] were prepared Thus, 2-(4-hydroxyphenyl)benzo[b]thiophene-6-ol was esterified with MeSO2Cl and the diester subjected to Friedel-Crafts acylation with 4-(2-piperidinoethoxy)benzoyl chloride to give I (R = R1 = MeSO2). This was saponified to give I (R = R1 = H) (II). Immature female rats administered 0.03 µg estradiol propionate (III) s.c. together with 3 mg II s.c. daily for 4 d had average uterus weight of 21.3 mg. Those given III alone had average uterus weight of 65.9 mg. I also were effective as antiandrogens and as mammary tumor inhibitors.

Ι

L6 ANSWER 32 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1983:422309 CAPLUS Full-text

DOCUMENT NUMBER:

99:22309

TITLE:

Acylated benzothiophenes

INVENTOR(S):

Peters, Mary K.

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

U.S., 7 pp. Cont.-in-part of U.S. Ser. No. 246,333,

abandoned.

CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 4380635	Α	19830419	US 1981-331046		19811216
CA 1167036	<b>A</b> 1	19840508	CA 1982-400262		19820331
EP 62505	A1	19821013	EP 1982-301739		19820401
EP 62505	B1	19850724			
R: AT, BE, CH,	DE, FF	R, GB, IT,	LU, NL, SE		
GB 2096608	Α	19821020	GB 1982-9681		19820401
GB 2096608	В	19850612			
DD 201794	<b>A</b> 5	19830810	DD 1982-238653		19820401
CS 227347	B2	19840416	CS 1982-2356		19820401
RO 84584	A1	19840717	RO 1982-107118		19820401
PL 130584	B1	19840831	PL 1982-235751		19820401
AT 14429	T	19850815	AT 1982-301739		19820401
DK 8201513	A	19821004	DK 1982-1513		19820402
FI 8201161	A	19821004	FI 1982-1161		19820402
JP 57181079	·A	19821108	JP 1982-56481		19820402
ES 511123	<b>A1</b>	19830216	ES 1982-511123		19820402
HU 28746	A2	19831228	HU 1982-1025		19820402
HU 191084	В	19870128			
SU 1138028	A3	19850130	SU 1982-3417251		19820402
PRIORITY APPLN. INFO.:			US 1981-246333	A2	19810403
			US 1981-246335	Α	19810403

The acylated benzothiophenones I (R,R1 = C1-4 alkyl, RR1 = polymethylene, AΒ CH2CHMeCH2CH2, CH2CH2OCH2CH2) were prepared by acylation-demethylation of benzothiophenes II. Thus, 3-MeOC6H4SN was treated with BrCH2COC6H4OMe-p followed by cyclization to give II, which was treated with AlCl3 and the acid chloride of 4-(2-piperidinoethoxy) benzoic acid to give I (NRR1 = piperidino).

L6 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1983:71918 CAPLUS Full-text

DOCUMENT NUMBER:

98:71918

TITLE:

Acylated benzothiophenes

INVENTOR (S):

Peters, Mary Kathleen; Jones, Charles David

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA

SOURCE:

Eur. Pat. Appl., 29 pp.

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
`	'			· <b>-</b>	
· EP 62505	A1	19821013	EP 1982-301739		19820401
EP 62505	B1	19850724			
R: AT, BE, CH,	DE, FR	, GB, IT,	LU, NL, SE		
US 4380635	A	19830419	US 1981-331046		19811216
AT 14429	${f T}$	19850815	AT 1982-301739		19820401
PRIORITY APPLN. INFO.:			US 1981-246333	Α	19810403
			US 1981-246335	Α	19810403
			US 1981-331045	Α	19811216
			US 1981-331046	Α	19811216
		•	EP 1982-301739	Α	19820401
OTHER SOURCE(S):	MARPAT	98:71918			

GΙ

3-[4-(2-Aminoethoxy)benzoyl]benzothiophenes I [R, R1 = C1-4 alkyl; RR1 = AB (CH2)4, (CH2)5, (CH2)6, CH2CHMeCH2CH2, CH2CH2OCH2CH2], useful as antiestrogens (no data), were prepared by acylating benzothiophene II. Thus, heating 3-MeOC6H4SCH2COC6H4OMe-4 with polyphosphoric acid gave II, which was acylated by 4-(Me2NCH2CH2O)C6H4CO2H.HCl and SOCl2 in PhCl-CH2Cl2 containing DMF and AlCl3 to give I (R = R1 = Me).

ANSWER 34 OF 34 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1983:71917 CAPLUS Full-text

DOCUMENT NUMBER:

98:71917

TITLE:

Benzothiophene compounds

INVENTOR(S):

Jones, Charles David

PATENT ASSIGNEE(S):

Eli Lilly and Co., USA Eur. Pat. Appl., 107 pp.

SOURCE:

CODEN: EPXXDW

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 62503	A1	19821013	EP 1982-301737	19820401
R: BE, CH, DE,	FR, GB	, IT, LU, NL	, SE	
AU 8282265	Α	19821007	AU 1982-82265	19820401
AU 555658	B2	19861002		
GB 2097788	Α	19821110	GB 1982-9680	19820401
GB 2097788	В	19850424		
JP 57181081	Α	19821108	JP 1982-56479	19820402
PRIORITY APPLN. INFO.:			US 1981-246335 A	19810403
			US 1981-331045 A	19811216

$$CO$$
 $OCH_2CH_2N$ 
 $Z$ 
 $OCH_2CH_2R$ 
 AB [(Aminoethoxy)benzoyl]benzothiophenes I (Z = CH2CH2CH2, CHMeCH2) were prepared, and limited the increase of uterine weight in rats treated with estradiol. Thus, treating II (R = Br) with 3-methylpyrrolidine in DMF containing KI gave II (R = 3-methyl-1-pyrrolidinyl) which was deprotected by NaOH to give I (Z = CHMeCH2).